CLINICAL AND PATHOLOGICAL

PAPERS

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THE VALUE OF ALCOHOL IN CARBOLIC ACID POISONING.

A CLINICAL AND EXPERIMENTAL STUDY.*

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1. *INTRODUCTION.*

The use of alcohol as an antidote in carbolic acid poisoning was first brought before the medical profession by Dr. Seneca D. Powell of New York City. At his clinical lectures, from about 1894 on, he was in the habit of demonstrating his theory by such an experiment as washing his hands in pure carbolic acid and then in alcohol, and had even filled his mouth with the pure acid, and by quickly rinsing it with 95 per cent. pure alcohol had experienced no harmful results. From these experiments he made the statement that alcohol is an antidote to carbolic acid, and suggested its being used internally in cases of poisoning. The results of his five years experience were reported to the Medical Society of the County of New York Feb. 27, 1899, and appeared in the reports of this society.[1] He, however, had had no practical experience in poisoning cases and goes no further than to mention a case of which he had heard of a one-month-old infant, who, after swallowing the strong acid, had been given a teaspoonful of whisky, though apparently moribund, and had recovered temporarily. Furthermore, this child, having died eight days later of pneumonia, showed no signs of an eschar in the stomach.

*** From the Medical Service of the Lakeside Hospital and the Pharmacological Laboratory of Western Reserve University.**

[1] Powell: Medical Record, New York, 1899, vol. lv, p. 372.

The first mention of alcohol as an antidote from a clinical standpoint is in the report by Donald B. Fraser[2] of a patient who took an ounce of the pure acid in a glass of whisky, and, though unconscious for eight hours, eventually recovered, repeated lavage with water having been resorted to. He then states that alcohol is apparently a true antidote in carbolic acid poisoning. Whether the author was familiar with Powell's work, at that time unpublished, he does not state.

The credit of first using alcohol in poisoning cases seems to be due to Dr. J. Drysdale Buchanan,[3] who used lavage with two quarts of 35 per cent. alcohol for a patient who had taken one ounce of the acid.

Since these early reports there have been a number of isolated cases in the literature from which the most positive conclusions have been drawn. For example, Kelly[4] in 1899, after reporting one successful case, states that "alcohol is undoubtedly the best antidote for all cases of carbolic acid poisoning, and, indeed, is an absolute antidote." Phelps,[5] on the strength of Powell's work, says: "In cases of carbolic acid poisoning, if immediately after the administration of the poison, alcohol was thrown into the stomach the poisonous effects of the carbolic acid would at once be neutralized." Pinkney,[6] after reporting a fatal case, says: "The amount of carbolic acid left in the stomach and intestines when alcohol came in contact with it was rendered harmless, and the general action of the already absorbed poison was checked immediately." Finally, Gross,[7] in discussing the subject, refers to alcohol as a chemical antidote, and says that the reaction forms "a new phenol benzine or aromatic compound having the chemical and therapeutic properties of alcohol."

Two years ago one of us, having been favorably impressed by some of these reports and by good results obtained by the use of alcohol by himself, and other members of the staff of the Johns Hopkins Hospital, in cases of carbolic acid poisoning, introduced the use of alcohol in the emergency room of the Lakeside Hospital. Since that time thirteen patients with carbolic acid poisoning have been admitted to the hospital, for all of whom the alcohol treatment has been used.

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[2] Fraser Ibid., 1899, vol. xlviii p. 741.
[3] Buchanan: Ibid., 1899, vol. lvi, p. 241.
[4] Kelly: Merck's Archives, 1899, p. 441.
[5] Phelps: New York Med. Jour., 1899, vol. lxix, p. 62.
[6] Pinkney: Amer. Med., 1901, vol. i, p. 358.
[7] Gross: Fort Wayne Med. Jour. Mag., 1899, p. 73.

2. *CLINICAL DATA.*

BY T. W. CLARKE.

As all former reports on this treatment have been of single cases, from which, owing to the natural tendency of the profession to report their successful cases only, but slight conclusions can be drawn, it has seemed advisable to report the present series of thirteen cases more or less in full. For permission to use these cases we wish to thank Drs. Hunter Powell, John H. Lowman, Henry E. Upson and Edward F. Cushing, visiting physicians to the Lakeside Hospital.

Case 1.—Patient admitted at 8 p. m. Dec. 14, 1903, unconscious. Had taken carbolic acid, ℥ss, in whisky. There were two burns on chin. Pupils react, breathing heavily. Pulse was so rapid and weak that it could not be counted. Stomach was washed out with two quarts alcohol, 10 per cent., then milk and eggs, Oi, left in stomach. Strychnin, 1/30 gr., digitalin, 1/30 gr., given hypodermically. At 9 p. m. patient was conscious and very noisy; quieted with sodium bromid and chloral, āāʒi, by rectum, and slept the rest of the night. Temp. 100, pulse 110, at midnight.

December 15: Some pain on swallowing. Nothing to be seen on examination of the throat and mouth. Temp. 99 to 101.5, pulse 80, resp. 20, urine dark.

December 16: Patient allowed up in wheel chair. Still slight soreness on swallowing. Physical examination negative. Temp. normal, pulse 70 to 80, respirations 20 to 26.

December 18: Eats well, no difficulty in swallowing. Scar on chin disappearing. Discharged, well.

Case 2.—Patient admitted 11 a. m. Jan. 17, 1904, having taken carbolic acid, ℥iss, shortly before, in glass of beer. Patient was unconscious. Pulse arrhythmic, rate 160. No burns on lips, slight erosion on cheeks. Lavage performed with alcohol, 10 per cent. The washing contained carbolic acid and much undigested food. Milk and eggs, Oi, added and left in. Artificial respiration was resorted to several times. Strychnin, 1/20 gr., and digitalin, 1/30 gr., were given twice in quick succession. Temp. 96.4, resp. 58, pulse 160. At 1:30 p. m. the pulse and respiration became most irregular. Strychnin, 1/20 gr., and digitalin, 1/30 gr., steadied both. Hot water bottles were applied and coffee, ℥viii, given *per rectum.* At 3 p. m. subcutaneous infusion of normal saline, 600 c.c., was given and repeated at 7 p. m., the last containing 7 gm. sodium sulphate. Patient vomited frequently between 4 and

5:45. Patient first showed consciousness at 7 p. m. while the infusion was being given.

January 18: Patient is doing well. Temp. 100.5 to 101, pulse 100 to 110, resp. 30 to 40. The patient looks well and seems but little the worse for her experience. Urine black, slight trace of albumin, no blood, no casts.

January 19: Last night the patient's temperature rapidly rose, and this morning was 105, resp. 70 and pulse 160. Leucocytes, 5,900. The patient is very cyanotic. Sponge baths, strychnin and oxygen ordered. Examination of chest is negative. Urine yellow, heavy trace of albumin, no blood, no casts.

January 20: The temperature has remained in the neighborhood of 105, pulse 150 to 170, resp. 60 to 65. To-day there is a definite pneumonia area over right upper lobe. Over the entire chest there are patches of tubular breathing and large mucous râles. Patient died at 10:30 a. m.

Autopsy showed an aspiration bronchopneumonia and a small, irregular, dark-colored patch in the fundus of the stomach.

Case 3.—Patient admitted March 4, 1904, 9 p. m. Walked in, said he had drunk three glasses of whisky and then carbolic acid (doubtful quantity). Was quite conscious and rational. On left side of mouth and lower jaw were acid burns. Inside of mouth and pharynx slightly burned. Respirations normal, 28; pulse good, 100 a minute; temperature normal. Stomach was washed with 10 per cent. alcohol, and water, and sent to ward. He showed practically no constitutional symptoms; slept all night after 1:30; pulse 98 to 104, but of good quality. The next day the inside of patient's mouth was blistered. Dicharged, cured.

Case 4.—Patient admitted May 9, 1904, 12:10 a. m. Brought in in ambulance in a delirious condition. Had been drinking and had then taken carbolic acid, ℥i. Pulse fairly good quality, 100 per minute. Some burns about the lips. The stomach tube was passed and food particles removed, smelling strongly of phenol. Lavage with 10 per cent. alcohol solution and followed with water. Milk, Oi, and 4 eggs inserted and left in stomach. Patient was given sodium bromid, 25 gr., and slept until morning. Temp. 96.6, pulse 100, resp. 24. The urine the next morning was black, contained a faint trace of albumin and a few hyalin casts, sp. gr. 1038. The next morning patient appeared well; slight eschar on lips; nothing to be seen in throat; some epigastric tenderness. Patient was kept in the ward until May 15 and then discharged, well.

Case 5.—Patient admitted 5:20 p. m. July 22, 1904. She had been drinking for five days, and at 5 p. m. of the day of admission drank 10 cents' worth of carbolic acid (℥i), with suicidal intent. She was taken into a saloon and became unconscious. On admission she was unconscious, cyanotic, breathing heavily, a great deal of mucus protruding from the mouth, vomiting a little. Pulse rapid and small. The face, mouth and pharynx were badly burned. Temp. 98, pulse 120, resp. 30. The stomach contents showed carbolic acid. Lavage with 10 per cent. alcohol, followed by water, and milk and eggs left in place. She was unconscious after reaching the ward, but regained consciousness at 8:20 p. m. Patient dozed all night, waking several times to vomit mucus. The temperature remained elevated for several days, 100 to 101 July 23, 99.5 to 100.5 July 24, 99 to 100 July 25, 26 and 27. The pulse remained at 120 until noon July 23 and then gradually came down to 100 that night, and was 80 on July 26. The respirations from 20 to 30 the first day, 20 after that. The urine was never obtained black, but contained a heavy trace of albumin and many hyalin and granular casts. The leucocyte count the day of admission was 18,400, reds 4,226,000, and hemoglobin 95 per cent. Patient discharged on July 27. The scars on her face were very sore and showed some signs of sloughing. Temperature was 99.

CASE 6.—Patient admitted 2:30 a. m. July 26, 1904. Had taken one ounce of carbolic acid in a glass of whisky. Became unconscious in five minutes, and was sent immediately to the hospital. On admission was unconscious, no sign of burns about mouth or lips; breathing stertorously; pupils small; pulse small, 120 a minute; no vomiting. Lavage with alcohol, 10 per cent., followed with water; after washing, milk and eggs and sodium sulphate, ℥ii, were put in through tube. Patient became conscious at 5 a. m. Recovery was uneventful. The urine was dark-brown, acid, sp. gr. 1014, and contained a few hyalin and granular casts. On admission temperature was 97 and rose to 100.2 at 8 a. m., then gradually came down to 99 July 28. Pulse on admission was 118, at night 100, and 70 on the night of July 27. Respirations 32 on admission, at noon 14, and after this 18 to 20. The leucocyte count the morning of admission was 19,500. Patient did well and was discharged July 28, well.

CASE 7.—Patient admitted 8:30 a. m. Sept. 14, 1904. Had taken carbolic acid, ℥i. She was unconscious, tongue and lips slightly burned, very weak, cyanosed, breathing stertorously, pupils much contracted. Pulse barely perceptible, quite irregular, 140 a minute. Stomach tube passed and contents showed carbolic acid. Lavage with alcohol, 10 per cent., and then water, eggs, milk and sodium sulphate, ℥i, by tube. Strychnin, 1/30, and digitalin, 1/30, given twice within an hour. Intravenous injection of soda sulphate, 2 per cent., 250 c.c. Patient became conscious in two hours. In the afternoon had severe vomiting spell, which was relieved by dilute hydrocyanic acid, 4 minims, and bismuth subnitrate, 10 gr. On admission temperature was 99, pulse 112 and resp. 30. Temperature went up to 100 that night, and then down to normal the following evening. The pulse remained at 110 for 24 hours, and then dropped to 80 and remained in that neighborhood, with occasional flare-ups. Respiration came down gradually from 30 to 20 in 3 days. The urine was pale, sp. gr. 1020, faint trace of albumin, and a very few hyalin casts. Patient suffered considerably from soreness of the mouth and had very little pain in the stomach. No vomiting after the first day. Discharged, well, Sept. 19.

Case 8.—Patient admitted Feb. 28, 1905. Child, aged 19 months, swallowed an unknown quantity of 95 per cent. carbolic acid three hours before admission. Seen by a physician at the home five minutes later, who washed stomach with alcohol and water. Patient was unconscious when seen at that time. On admission was very drowsy, temperature 101.5, pulse 160. Tongue, pharynx and inside of cheeks very badly burned, white in color. On admission patient was given magnesium sulphate, ʒii, and strychnin, gr. 1/250. March 1, temp. 104, pulse 152, resp. 40. March 2, temp. 100, pulse 100, resp. 20. From then on the temperature varied from normal to 100, pulse from 100 to 150. and respirations from 25 to 30. The child did well, and on March 6, the mouth having healed, patient was discharged.

Case 9.—Patient admitted on March 23, 1905. The history was that she apparently fainted in an elevator, and poisoning was not suspected for one and a half hours. On admission she was moribund, unconscious, cyanotic, resp. 36, pulse small and weak, 160, pupils dilated, faint trace of carbolic to breath, mucous membranes, gums and palate white. Patient was stimulated with strychnin, 1/20 gr., digitalin, 1/30 gr., and stomach washed with alcohol, 10 per cent., and eggs and milk and magnesium sulphate, ℥iii, left in the stomach, 500 c.c. Soda sulphate, 2 per cent. solution, given intravenously. Patient never rallied and died half an hour after reaching the ward.

Case 10.—Patient admitted May 5, 1905, in an unconscious condition. Had taken carbolic acid, time not known. Severe burns of the cheek, corner of mouth, lips, tongue and roof of mouth. Pulse weak and rapid. Stimulated with strychnin and digitalin. Stomach washed with 10 per cent. alcohol and water. Eggs and milk, magnesium sulphate, ℥i, and sodium sulphate, ℥ss, inserted through tube. Temp. 100, pulse 110, resp. 20. Patient was restless after getting to ward, but later slept. Temperature during the day rose to 100.8 and pulse 120, but on the second day temperature became normal and pulse 80. The leucocytes on May 5 were 28,200. Patient had difficulty in swallowing and considerable epigastric tenderness.

On May 7 patient felt well except for the burns on the face, and insisted on going home.

Case 11.—Patient admitted, unconscious, 9:30 p. m. June 1, 1905. Had taken carbolic acid, ℥ii, a few minutes before.

Two scars, 4 cm. long, on upper lip; slightly cyanotic; pulse good. Lavage, 10 per cent. alcohol, then magnesium sulphate and eggs and milk by stomach tube. No stimulation. Consciousness returned 10:30 p. m. Next day scars marked on lip and slight on roof of mouth and tongue. Large white patch on right tonsil and posterior wall of pharynx. Larynx inflamed, abdomen rigid and sensitive in upper half. Blood examination: Leucocytes, 11,800; hemoglobin, 83 per cent.; fresh blood normal. Urine greenish, sp. gr. 1020, acid, loaded with hyalin, granular and leucocyte casts. June 4 and 5: Urine, sp. gr. 1015, neutral, no casts. June 5: Discharged, well.

Case 12.—Patient admitted 3:30 p. m. Sept. 7, 1905. Had taken carbolic acid, ℥i diluted with a little water, fifteen minutes before. She had not swallowed all, as the glass was knocked from her hand after two swallows.

Patient was comatose, cyanotic, Pupils at first dilated and then pinpoint. Pulse very weak. There were two scars on the lips and the entire mouth and tongue was whitened, on the chest and abdomen was very extensive burn, extending from the neck to the pubes. The treatment consisted of lavage with 10 per cent. alcohol and the introduction of yolk of eggs and sodium sulphate ℥ii. Strychnin 1/20 gr. and digitalin 1/20 gr. were given hypodermically. The patient regained consciousness in two hours and was quite violent for a short time, then quieting down. The next day the urine was of the characteristic brown-black color sp. gr. 1005, for three days contained a few hyaline and granular casts; after this it was normal. The temperature remained slightly elevated for five days, 99 to 101.5. For two days there was some pain in the mouth, especially on swallowing. By the fifth day the mouth had cleared up, but the skin burn was still very sore, red and blistered. The patient was discharged well on the ninth day.

Case 13.—Patient admitted 8 a. m. Sept. 14, 1905. Had taken carbolic acid ℥i in water fifteen minutes before admission. Semi-conscious, cyanotic on admission. Burns on lips and togue. Lavage with alcohol 10 per cent. Magnesia sulphate ℥ii, two eggs and milk by tube. Strychnin 1/20 gr., digitalin 1/25 gr. hypodermically. Temperature 100, pulse 98; next day pulse and temperature normal. Discharged well September 16.

An analysis of the preceding cases shows several interesting features. The local effect on the mouth is greater if the acid is taken pure or in water than if taken in alcohol, all ten cases of the first class showing local eschars, whereas two of the three of the latter class showed no burns whatever. All the cases were unconscious on admission, except two who had taken the drug after drinking whisky and one who had taken it in water. This includes the cases which had taken the poison in whisky and beer. The longest period of unconsciousness occurred in the patient who had taken the acid in beer. The average period of unconsciousness of the cases having taken the drug in alcohol was three and three-quarters hours and of those in which no such history was obtained was one and three-quarters hours. The mortality record was low, only two of the thirteen cases having died, one of these from bronchopneumonia a few days afterward, probably due to an inhalation of material during the lavage, which was performed with difficulty, and the other having been admitted moribund after having been kept for two hours outside without treatment. The treatment in all the cases consisted in a most thorough lavage with 10 per cent. alcohol and in the later few cases this was followed by lavage with plain water. In eleven of the cases milk and eggs were introduced through the tube and left in the stomach. Sodium sulphate was administered through the tube in three cases and intravenously in three cases and magnesium sulphate in the stomach in four cases. Stimulation with strychnin and digitalin was resorted to in eight cases.

CASES TREATED WITHOUT ALCOHOL.

A study of the records of the fourteen cases of carbolic acid poisoning treated at the Lakeside Hospital previous to the introduction of the use of alcohol in treatment surprised the authors by their similarity to their own results. In this series of fourteen, all of which were treated by thorough lavage, either with plain water or a solution of magnesium sulphate, there were only three deaths, two of these due to pneumonia and the third a case admitted ten hours after taking two ounces of the acid, an emetic of magnesium sulphate having been resorted to, but no lavage performed. In this early series also the cases which had taken the poison in alcoholic beverages seemed to show a greater tendency to unconsciousness than those that had taken it pure or in water. In the ten cases in which the record was made as to the manner in which it was taken, five took it with alcohol and five either pure or in water. Of the five alcoholic cases four were unconscious and one semi-conscious, while of the five that had not used alcohol two were unconscious, one semi-conscious and two conscious.

CASES COLLECTED FROM THE LITERATURE.

The following cases have been collected from literature, and though many of the reports are too meager for any conclusions to be drawn from them, they are inserted that the reader may see the various ways in which alcohol has been used in carbolic acid poisoning in recent years. It will be noticed that they are all of isolated cases.

In these cases the following abbreviations will be used:

S. and A. Sex and age.
P. Amount of poison and how administered.
T. Time elapsed before treatment.
L. Local eschars.
Sy. Symptoms.
Tr. Treatment.
C. Time elapsed before consciousness returned.
A. After history.
R. Results.

CASE 1.—Fraser,[2] 1895. S. female. R. phenol, ℥i, in whisky. T. 15 min. L. none. Sy. coma. Tr. atropin hypo. lavage. C. 8 hours. A. vomited 24 hours. R. well.

CASE 2.—Buchanan,[3] 1899. S. and A. female, 35. P. phenol, ℥i. T. short. Tr. sodium sulphate hypodermic, lavage with 2 quarts of 35 per cent. alcohol. R. well.

CASE 3.—Adams,[8] 1899. S. and A. female, 36. Tr. alcohol 1 pint, by mouth; alcohol, ℥iv, and whisky, ℥iv, q. 15 min. Six doses whisky, ℥ii q. h. 8 doses. R. well.

CASE 4.—Kelly, 1899. A. 21 months. P. phenol, ℥i. T. 6 min. Tr. olive oil. Alcohol, ʒvi. Apomorphin, 1/30 gr. Whisky, ʒi, q. 10 min. Eight doses. C. 30 min. R. well.

CASE 5.—Klein,[9] 1900. S. and A. female, 29. P. phenol, ℥ii. Tr. alcohol, ℥iv, by mouth q. ½ hours, 4 doses, then ʒi q. i hour, 4 doses. Morphia, ¼ gr. R. well.

CASE 6.—Rodman,[10] 1900. S. and A. female, 60. P. phenol, ℥ii, pure. T. short. L. lips and tongue. Sy. coma, cyanosis, subnormal temperature. Tr. alcohol, ℥iv, into pharynx, then lavage with warm water and then with dilute alcohol. A. temperature for 2 days, 101 to 102. R. well.

CASE 7.—Pinkney,[6] 1901. S. and A. female, 3½ years. P. phenol, ʒiv. T. ½ hour. L. lips and chin. Sy. coma, cyanosis, thready pulse. Tr. alcohol, ℥iiiss. Strychnin, hypodermic, 1/30 gr. Infusion normal saline, 1 pint. C. 7 hours. A. temperature rose rapidly to 106. R. death in 12 hours.

CASE 8.—Gries,[11] 1901. S. and A. female, 3. Sy. coma,

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8. Adams: N. Y. Med. Jour., 1899, vol. lxx, p. 780.
9. Klein: Jour. Am. Med. Assoc., 1900, xxxv, p. 1557.
10. Rodman: Med. Record, N. Y., 1900, vol. lviii, p. 70.
11. Gries: Therapeutic Gazette (Detroit), 1901, vol. xxv, p. 587.

weak pulse, cyanosis, appeared moribund. Tr. Hypodermic of ether. Magnesium sulphate, 1½ quarts, by stomach tube, then lavage with 20 per cent. whisky and ℥iv left in. Atropin, 1/200 gr. Strychnin, 1/40 gr., hypodermic. C. few hours. R. well.

CASE 9.—McDonald,[12] 1902. P. phenol, ℥i. T. 25 min. Sy. collapse, coma. Tr. stomach tube, alcohol, Oi left in a few minutes and siphoned off. This repeated once. Then lavage with water, whisky, ℥iv, nitroglycerin, 1/100 gr., strychnin, 1/20. C. six hours. R. well.

CASE 10.—King,[13] 1902. S. and A. female, 33. P. phenol, ℥ss. 3 min. Tr. alcohol, Oss. Then lavage with water, repeated. Alcohol, ℥iii, left in. C. 4 hours. R. well.

CASE 11.—Marshall,[14] 1903. S. and A. male, 74. P. phenol, ℥i, and olive oil, ℥iv, per rectum. T. immediate. Sy. coma, pulseless. Tr. irrigation with 2 quarts of water 1 hour and 10 minutes. Alcohol and water, āā℥iv, repeated and irrigated. C. 8 hours. R. well.

CASE 12.—Atwell,[15] 1903. S. and A. female, 35. P. phenol, ℥ss, in water. T. 20 min. Sy. coma, cyanosis, weak pulse. Tr. atropin, 1/50 gr., hypodermic. Dilute alcohol, ℥vi. Lavage with water, gallon 1. Alcohol, 95 per cent., ℥vi. Lavage in 5 minutes. Magnesium sulphate, ʒi, in water Oi. Stimulation. Infusion normal saline. R. well.

These two facts shown by a study of our own cases, namely, the immaterial difference in the mortality, whether the stomach was washed with alcohol or with some other liquid, and the apparently greater constitutional symptoms when the drug was taken with alcohol then when taken clear or in water, seemed to throw such grave doubts on the antidotal power of alcohol to carbolic acid when taken internally, and these doubts agreeing so well with the opinions expressel in the recent textbooks on toxicology, the authors determined before publication to undertake some experimental work in the effort to prove or disprove the antidotal action.

3. *EXPERIMENTAL DATA.*

BY DRS. BROWN AND CLARKE.

Acting under the direction of Dr. Torald Sollmann, a series of animal experiments were carried on in the pharmacological laboratory of the Western Reserve University, the results of which are herewith published.

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[12] McDonald: Fort Wayne Med. Jour. Mag., 1902, xxii, p. 59.

[13] King: New Orleans Med. and Surg. Jour., 1902, vol. liv, p. 740.

[14] Marshall: Med. Record N. Y., 1903, vol. lxiii, p. 174.

[15] Atwell: Virginia Med. Semi-Monthly (Richmond), 1903, vol. viii, p. 73.

INTRODUCTION.

Some experimental investigations of the subject have been undertaken by others, but these are rather unsatisfactory; the number of animals used by each investigator seems rather too limited to make the conclusions binding.

In 1901 Thornton[16] made some experiments on a series of five dogs, giving by stomach from one to four drams of phenol, undiluted, or with alcohol or oil. This was left in the stomach, together with the antidote. He gave to one animal phenol mixed with 95 per cent. alcohol, and after the onset of toxic symptoms administered more alcohol. The result was death in four hours, with no signs of improvement. Another animal was given phenol mixed with oil, which gave practically the same result. In the remaining animals phenol was administered and, after the poison symptoms had become manifest, alcohol in single or repeated doses was given without any beneficial effect.

The following year Wallace[17] made observations on two rabbits and two cats. The first rabbit was given the lethal dose (0.6 gm. per kilo) subcutaneously, resulting in death in one hour and ten minutes. The second rabbit was given 5 cc. of 60 per cent. alcohol subcutaneously and this followed five minutes later by the same dose of phenol as was given the other rabbit. The toxic symptoms appear after the same interval of time as in the first rabbit. Five cc. doses of the diluted alcohol were injected at intervals, without improvement of the condition. The animal died in one and one-fourth hours.

The cats were given the lethal dose by stomach, one receiving the aqueous solution and the other receiving the phenol in 60 per cent. alcohol. Alcohol was later injected subcutaneously, but without effect. Both animals died after nine hours.

Method of Investigation.—Our experiments may be divided into three groups:

1. Systemic antagonism (intravenous injection).
2. Antagonism in the stomach (5 per cent. phenol).
3. Efficiency of lavage (undiluted phenol).

I. SYSTEMIC ANTAGONISM.

For the purpose of determining whether alcohol can lessen or abolish the systemic effects of phenol, a 1 per cent. solution was injected intravenously into dogs, the dose of 1 c.c. per kilogram (0.01 gm. of phenol) being repeated every minute. Three solutions of phenol were employed—one in normal saline solution, the second in 10 per cent. alcohol, and the third in 20 per cent alcohol, the results produced by these solutions being compared.

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[16] **Thornton: Progressive Med., Dec. 1901, p. 343.**

[17] **Wallace: N. Y. University Bul. of the Med. Sci., 1902, vol. ii, p. 58.**

Operative Methods.—All dogs used in these experiments were first given sufficient morphin to render them quiet and then kept under complete ether anesthesia during the course of the experiment. Before coming out of the anesthetic condition they were killed.

A cannula was placed in the trachea, through which the anesthetic (ether) was afterward given, and a cannula in the carotid for blood pressure tracings. The intravenous injections were made through a cannula placed in the femoral vein and connected with a graduated burette which contained the injection solutions.

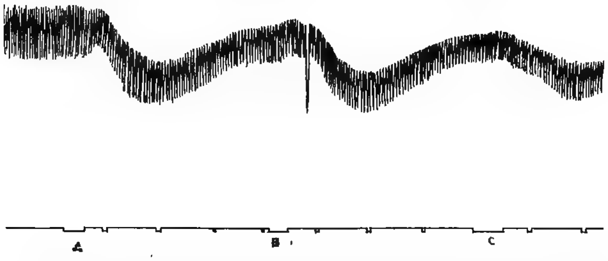

Fig. 1.—Intravenous injections of 1 c.c. per kilo of 1 per cent. phenol in normal saline at A, B and C. Time marks 15 seconds.

(*A*) *Effects of Phenol in Normal Saline.* These will be described first for the purpose of comparison.

Blood pressure, and in some cases respiratory tracings, were taken. In all the animals the intravenous injection causes a *fall of blood pressure* which has a tendency toward recovery, depending on the quantity injected (Fig. 1.) Th. Gies[18] obtained the same results in his experiment with animals. The average fall is from 20 to 30 mm. of mercury. The fall begins almost immediately after the injection; reaches the minimum in thirty seconds and returns to about normal after sixty seconds. Each successive injection becomes less effective, with a tendency toward a slow gradual fall of blood pressure. Where the lethal dose is injected there is a rapid fall which terminates by stoppage of the heart (Fig. 2.).

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[18] Gies: The Archiv. für Exp. Path. and Pharm., 1880, vol. xii p. 401.

Respiration is but little affected except by the mechanical interference of the convulsive movements.

Onset of Convulsive Movements.—In all the animals employed the intravenous injection causes a gradual onset of convulsive movements beginning with a tremor of the legs and jaw, which gradually increases until the contractions acquire a clonic convulsive character. The absence of a rise of blood pressure which is usually associated with convulsions is probably due to the deep anesthesia and to the rather mild type of the convulsions.

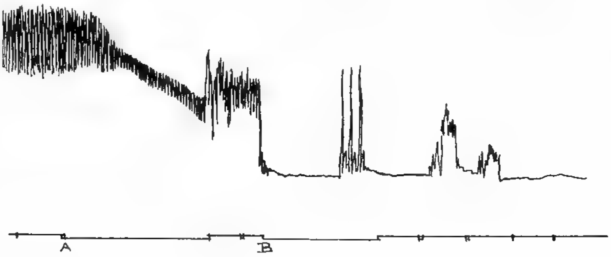

Fig. 2.—Death from intravenous injection of phenol. Injection made at A.

(*B*) *Effects of Alcoholic Solutions of Phenol.*—These do not differ from those of the saline solution of phenol in either quality or quantity. This is shown by Table 1.

TABLE 1.—Intravenous Injection. (Dog).

Dog. No.	Solvent.	Fall of Blood Pr. after first injection.	Twitching movements after c.c. per kilo.
1	Normal saline...	30 mm.	5 c.c.
4	Normal saline...	40 mm.	5 c.c.
2	10 p. c. alcohol..	24 mm.	3 c.c.
3	20 p. c. alcohol..	40 mm.	5 c.c.

II. ANTAGONISM IN THE STOMACH.

To determine the possibility of an antagonism in the stomach, the phenol was administered by stomach tube to rabbits. The just fatal dose (0.6 gm. per kilo.) was given, as a 5 per cent. solution in water, and in 10 per cent. alcohol and in 10 per cent. glycerin. These animals were not anesthetized.

(*A*) *Effects of the Watery Solution.*—The first symptoms start in one to three minutes and consist in a general trembling of the body and legs. The legs grow weaker and the animal falls on its side. Convulsive movements of a clonic type then appear, varying somewhat in intensity; the legs may become extended and rigid, while in some cases the head is thrown backward. Death occurs in from twenty-six minutes to six days.

The alcoholic and glycerin solutions produced the same effect quantitatively and qualitatively. This is shown in Tables 2 and 3.

TABLE 2.—DETAILS OF STOMACH EXPERIMENTS ON RABBITS.

Rabbit No.	Weight in Gms.	Amount of Phenol Given (always 0.6 gm. per kilo).	Diluent used.	Time Elapsed Before Appearance of Convulsive Movements.	Final Result.
1	920	11	Water.	1 m. 45 sec.	Died after 28 min.
7	770	..	Water.	....	Tube passed into trachea.
8	490	5.5	Water.	1 m. 30 sec.	Died after 25 min.
9	980	11.7	Water.	1 m. 30 sec.	Died after 6 days.
10	770	9.2	Water.	2 m. 10 sec.	Died after 8 hrs.
3	870	10.4	10 p. c. alc.	1 m. 50 sec.	Died after 24 hrs.
5	920	11	10 p. c. alc.	6 m. 30 sec.	Died after 3 days.
12	730	8.7	10 p. c. alc.	3 m. 15 sec.	Died after 18 min.
13	670	8	10 p. c. alc.	2 m. 30 sec.	Died after 2½ hrs
*2	830	10	10 p. c. glyc.	1 m. 40 sec.	Died after 3½ m.
4	1450	17.5	10 p. c. glyc.	2 m. 45 sec.	Survived.
6	1200	14.4	10 p. c. glyc.	3 m. 30 sec.	Survived.
11	780	9.3	10 p. c. glyc.	2 m. 10 sec.	Died after 2 days.

* It was thought some of the solution was aspirated into the trachea in this animal.

TABLE NO. 3.

TIME OF DEATH IN STOMACH EXPERIMENTS. (Rabbits.)

Phenol dissolved in				
Water	25 minutes	28 minutes	8 hours	6 days
Alcohol	18 minutes	2½ hours	24 hours	3 days
Glycerin	3½ minutes	2 days	Survived	Survived.

Microscopical Examination of the Stomachs.—This was undertaken by Dr. W. W. Williams in rabbits 1, 2, 3, 8 and 12. The findings may be arranged, according to the severity of the lesions, as follows:

Rabbit No.	Lesion.	Medium in Which Phenol was Administered.	Time Elapsing Before Death.
1	None	Water	28 minutes
8	Very slight	Water	25 minutes.
2	Fairly marked	Glycerin	3½ minutes.
3	Very severe	Alcohol	24 hours.
12	Very severe chronic gastritis (probably not due to the drug).	Alcohol	18 minutes.

It is seen that the local lesions are quite as severe with the glycerin or alcoholic solution as they are with the watery solution.

From these results it is evident that the alcoholic solution is no less toxic than the aqueous solution; while

TABLE NO. 4.

EXPERIMENTS ON STOMACH OF DOGS.

Dog Number.	Weight. (Kilo.)	Solvent Used.	Time in Stomach.	Initial Bl'd Pressure.	Blood Pressure 10 m. After Giving.	Blood Pressure Remains at Low Level.	Blood Pressure at End of Experiment.	Convulsions Ceased.	Duration of Experiment.	Result.	REMARKS.
10	14.	(Control)	....	106	72	Until death..	....	At death..	2 hrs., 45m.	Died......	Died.
5	4.	Water...	10m	102	37	1 hr., 27 m...	102	2 hours....	4 hrs., 12m.	Recovered.	Animal killed.
9	3.6	Water...	9m	105	43	30 minutes...	96	1 hr., 20m.	2 hours....	"	Died from ether.
6	8.	Alcohol..	10m	98	60	34 minutes...	60	1 hr., 40m..	4 hrs., 25m.	"	Animal killed.
8	6.	Alcohol..	10m	101	30	15 minutes...	100	3 hrs., 10m.	4 hrs., 29m.	"	Died from ether.
7	7.3	Alcohol..	10m	89	30	Until death.	20	At death..	46 minutes.	Died......	Tube did not enter stomach in washing.

the glycerin solution appears to be rather less fatal than the others, since two of the animals recovered completely. This might be due to slower absorption; for we are loathe to attribute it to any antidotal properties, either chemical or physiologic.

III. EFFICIENCY OF LAVAGE.

To determine the effect of lavage after the administration of concentrated phenol, and the relative value of water and diluted alcohol for this purpose, we employed dogs, anesthetized with morphin and ether, and connected for blood-pressure tracings. A stomach-tube was inserted and the stomach washed with water until the washings returned clear. One c.c. per kilo. of 95 per cent. phenol was then introduced through the tube and allowed to remain for ten minutes, when lavage was started, either with water or with 10 per cent. alcohol.

(*A*) *Effects of Concentrated Phenol by Stomach Without Lavage.*—This was tested on one animal. This showed an immediate fall of blood pressure amounting to 40 mm. of mercury. The pressure remains about constant after this primary fall, with a tendency toward a slight gradual fall, which continues until death. At no time during the experiment was there any evidence of improvement in the condition.

(*B*) *Lavage.*—In those animals in which lavage is employed, the blood pressure begins to rise after an interval of time which varies with different animals. The convulsive movements cease and the animals show all signs of recovery, the condition being judged by the blood pressure and convulsive movements.

The results are shown in Figure 3. They are identical for all the experiments, whether water or alcohol was used for lavage.

The details of the experiments are shown in Table 4.

4. *THE LOCAL ANTAGONISM OF CARBOLIC ACID AND ALCOHOL, AND OTHER PHENOL—SOLVENTS.*[19]

It will be recalled that the employment of alcohol in phenol poisoning was originally based on the local antagonism of the two drugs. This antagonism, as is well known, can be easily demonstrated, by dipping the finger in carbolic acid and then washing it at once with strong alcohol. To secure a complete removal of the phenol effects, however, it is essential that the application of the phenol should be of short duration, and followed very quickly by the alcohol. This is illustrated by the experiments of Wallace.[17] For instance, when the alcohol was used immediately, it removed all the effects completely; when it was used after ten minutes it removed the superficial whitening of the skin, but not the deep effects. When it was used after thirty minutes it had almost no effect. The addition of a small quantity of alcohol to the phenol increases its local effects—an observation which effectually refutes the theory that alcohol and carbolic acid enter into an innocuous chemical combination. The increased effect is to be explained by a more rapid absorption of the slightly diluted acid.

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[19] This chapter was kindly furnished by Prof. T. Sollmann, by whom the experiments were performed.

Wallace attributes the antagonism to the solvent action of alcohol on the phenol which would remove it much more readily from the superficial layers of the skin than would water. If the theory be correct, other phenol solvents must produce the same effect as alcohol. Wallace tested this with chloroform, ether and benzol, with positive results.

We made the following experiments, using somewhat different solvents:[20]

EXPERIMENT 1.—(*a*) The finger tips are plunged for thirty seconds into liquefied (95 per cent.) phenol, then for five minutes into the solvents. At the end of this time the finger in water is blanched, the fingers in 50 per cent. alcohol, 50 per cent. glycerin, ether and cottonseed oil appear normal. (*b*) The fingers are again dipped in the carbolic acid for one minute, then for one minute in the solvents.

The blanching is very conspicuous in water; then follows the 50 per cent. glycerin, then the 50 per cent. alcohol and ether.

The sensory effects are greatest in water, ether and 50 per cent. alcohol; less in 50 per cent. glycerin and oil.

EXPERIMENT 2.—The fingers are dipped into liquid carbolic acid for one and one-half minutes, then into solvents and observed at end of (*a*) one minute, (*b*) two and three minutes.

(*a*) One minute in solvents: The blanching is by far the most conspicuous in water; then follows the 25 per cent. glycerin and 25 per cent. alcohol. Turpentine and cottonseed oil appear normal. Burning is felt in the water, and in the glycerin and alcohol solutions, not in turpentine and oil. The water finger also shows the greatest anesthesia.

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[20] In all the experiments the subject was not aware of the nature of the solvent, the containers being numbered and the results tabulated by these numbers.

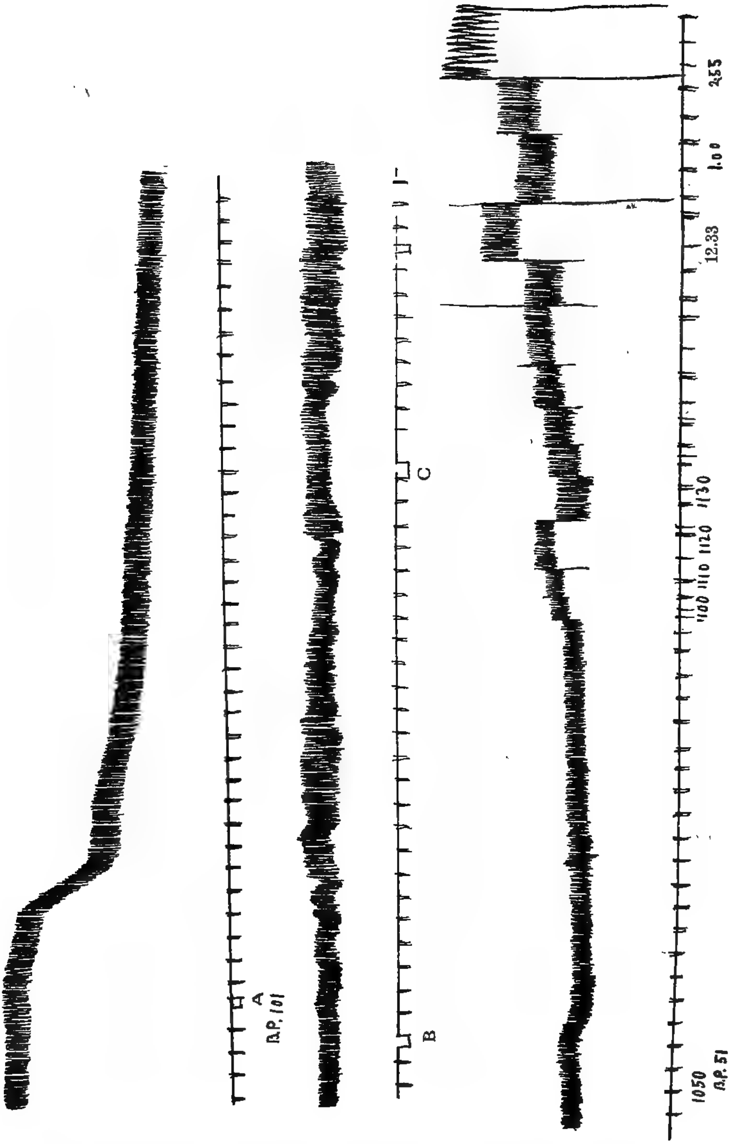

Fig. 3.—One c.c. per kilo of 95 per cent. phenol introduced into finished lavage at C. Blood pressure at end of experiment 100, the stomach at A, time 10 :25. Began lavage at B, time, 10 :35, time, 2 :55 Base line corresponds to 0 pressure.

(*b*) Two or three minutes in solvents: The blanching is most pronounced in the water; then follows 25 per cent. glycerin, then 25 per cent. alcohol. None is seen in turpentine and oil.

(*c*) The finger which had been put in water and which was still very much whitened, is rinsed in 95 per cent. alcohol. The blanching disappears almost completely at once.

(*d*) On the following day the skin of the fingers is rough and broken, and this condition persists for several days. It is alike in all the fingers.

It may be concluded that all phenol solvents arrest the local action of the phenol, i. e., the blanching action. This and the observation that dilution of the alcohol greatly impairs its efficiency sufficiently show that the effect is mainly due to solution and is not chemical. The solvents also tend to lessen the burning sensation, probably by removal of the phenol. They appear to be quite unable to prevent the late effects of the phenol, which may be attributed to the phenol which had already penetrated deeply when the solvent was applied.

It appeared interesting to determine also whether these solvents exert any effect when the carbolic acid is left in contact with the skin. For this purpose 5 per cent. solutions of phenol were made in various solvents. These were arranged in five small beakers, so that all the fingers of the left hand could be inserted and withdrawn simultaneously. The degree of blanching, tingling and anesthesia was compared after five minutes. The tingling sensation proved to be too irregular to be of any value for comparison. As in the previous series, the nature of the solvents were unknown to the experimenter and compiler until the conclusions had been drawn.

EXPERIMENT 3.—Comparison of 5 per cent. phenol in water (W), 10 per cent. alcohol (A), 10 per cent. glycerin (G), and cottonseed oil (O).

Experiments on two persons gave identical results:

The anesthesia was most conspicuous in W; somewhat less in A, absent in G and O.

The blanching was marked and about equal in W and A, almost absent in G, quite absent in O.

EXPERIMENT 4.—Comparison of 5 per cent. phenol in water, 25 per cent. alcohol, 25 per cent. glycerin, turpentine and cottonseed oil. The experiment was repeated on nine persons, with the following results:

Anesthesia.	Most Marked.	Less Marked.	Absent.
Water	7 cases	1 case	1 case.
Alcohol	2 cases	3 cases	4 cases.
Glycerin	None	1 case	8 cases.
Turpentine & Oil	None	None	9 cases.

BLANCHING

	Most Marked.	Second Place.	Third Place.	Fourth Place.	Absent.
Water	9 cases	None	None	None	None.
Alcohol	None	5 cases	2 cases	None	2 cases.
Glycerin	None	3 cases	3 cases	None	3 cases.
Turpentine	None	None	2 cases	3 cases	4 cases.
Oil	None	None	None	None	9 cases.

TINGLING.

	Most Marked.	Second Place.	Third Place.	Absent.
Water	1 case	None	None	8 cases
Alcohol	3 cases	None	None	6 cases
Glycerin		1 case	None	8 cases
Turpentine		None	None	9 cases
Oil	1 case	None	1 case	7 cases

These results show that the addition of all the solvents diminishes the local effects of phenol. The effect on the tingling sensation is, however, irregular. This may be attributed to the difficulty of exact observation. The effect is more pronounced on the superficial action (blanching) than on the deeper actions (anesthesia). Oil alone prevents both actions in all cases. Then come, in order of efficiency, turpentine, 25 per cent. glycerin, and 25 per cent. alcohol. Glycerin is more effective, for the same degree of dilution, than is alcohol.

In this experimental arrangement the effect of the solvents can not be explained, as in the previous series, by removal of the phenol. Nevertheless, it seems to be connected with their solvent power. It may be explained in the following manner: If a substance is introduced into a mixture of two immiscible solvents, a and b, it will be distributed between these two solvents in a ratio proportional to its solubility in a and b. If it is more soluble in a, this will contain a greater amount. This may be demonstrated by shaking a 1 per cent. solution with an equal volume of olive oil in one test tube, and with an equal volume of petroleum benzin in another. If a little ferric chlorid solution is added to both test tubes, the watery layer will not be colored in the oil tube (the phenol having passed into the better solvent), while it will be colored a deep violet in the benzin tube. The benzin being a poor solvent, almost all of the phenol has remained in the water.

In our experiment, the fluids of the tissues constitute one solvent, the fluid in which the carbolic acid is applied the other. The better the solvent power of our solvent, the less of the carbolic acid will pass into the tissues.

In the case of alcohol, and to a lesser extent with glycerin solutions, some of the solvent is doubtless absorbed into the tissues, which explains the relative inferiority of these to turpentine, and especially to oil, which are absorbed much more slowly.

These experiments contradict the rather prevalent opinion that the absorption of phenol is quickened by alcohol and perhaps also by glycerin. As far as we know, this opinion is purely theoretical. It may be true as far as the addition of small quantities of these substances are concerned, which would then act, not so much as solvents, but by increasing the fluidity of the phenol—a very important factor in absorption. It might theoretically hold also for the alimentary canal, since these solvents are absorbed there with considerable rapidity. This view is supported by the clinical experiences, although our experiments on rabbits (Series 2) can scarcely be interpreted in its favor. As concerns the skin, the experimental results constitute a positive refutation of the quicker absorption of alcoholic solutions in this situation.

The relative inferiority of alcohol to the other solvents is not sufficient to be of importance; while its greater fluidity and its miscibility with water constitute practical advantages more than sufficient to counterbalance the theoretical deficiencies. In emergencies, however, the value of the other solvents, particularly oil, should be borne in mind. It is interesting to note that the use of the latter antidote preceded that of alcohol.

GENERAL CONCLUSIONS.

From the above experiments the following conclusions may be drawn:

1. Alcohol has a local antidotal effect to carbolic-acid burns, due to its solvent action.

2. There is no evidence of chemical antagonism between alcohol and phenol.

3. There is no effect produced by alcohol on carbolic-acid poisoning after the latter has been absorbed into the system, as is shown by the intravenous experiments on dogs.

4. Alcohol and phenol placed in the stomach give no different results from phenol alone.

5. Lavage with alcohol is effective when the phenol is in the stomach, but its superiority over lavage with water is not pronounced.

From the clinical aspect it appears that alcohol has a local antagonism to carbolic acid. When the latter is taken in whisky the feeling of discomfort is less marked, and the local eschar is absent or but slightly evident. In cases of poisoning, lavage with alcohol is apparently an effective method of treatment. This is borne out by a comparison of thirteen cases here reported with a mortality of 15 per cent., with the collection made by Falck[21] in 1868 of forty-six cases in which the acid was taken internally with thirty-five deaths, a mortality of 65 per cent. On the other hand, the fourteen cases treated at the Lakeside Hospital by lavage prior to the use of alcohol with three deaths, a mortality of 21 per cent., give results so nearly akin to the alcohol cases that it would appear that the lavage were the dominant factor rather than the alcohol. When it is considered that it was only in the early nineties that stomach washing came into general use, and even later that the fear of its use in cases of corrosive poisoning was overcome, it seems probable that the good results in carbolic-acid poisoning from the use of alcohol, during the past few years, were due to the lavage and not to any antidotal property of the alcohol.

The authors do not wish to be interpreted as considering that alcohol is of no value in cases of carbolic-acid poisoning. *A priori* its solvent action and a slight tendency in the experiments with phenol in the dog's stomach, to an earlier rise in blood pressure, when the stomach is washed with an alcoholic solution, than when water is used, point to its value as a means of removing the poison from the stomach. From abundant clinical evidence, both in their own experience and in literature, it would appear to them to be an aid, when properly used, in the saving of life. On the other hand, this same solvent property, and the more marked symptoms of intoxication, when the poison has been taken in whisky, seem to establish a contradiction to the alcohol being used as an antidote and left in the stomach.

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[21] Falck: Ref. Blyth. Poisons. Their Effects and Detection. Wood's Library, 1885, p. 146.

The procedure recommended is immediate, abundant lavage with 10 per cent. alcohol, this to be followed by lavage with plain water, and stimulation as indicated. The point to be borne in mind is that alcohol is not effective after the carbolic acid has been absorbed and, to be of value, must be used while the poison is still in the stomach.

The other common methods of treatment of phenol poisoning are now being investigated, and the results will be communicated later.

The fact that three of the five fatal cases in the Lakeside Hospital series died of pneumonia, and one, at least, of these of a definite bronchopneumonia of the inhalation type, has impressed the authors with the necessity of care in the method of performing lavage in this class of cases. With the patient lying on his back, in a comatose condition, with the gastric contents regurgitating around the outside of the stomach tube, it is a simple matter for material to enter the larynx and set up an inflammatory process in the lung. To overcome this danger, the authors recommend, immediately after the tube is passed, to turn the patient on his side or face, with the head low, thus allowing any fluid in the pharynx to escape through the mouth. Since this method has been used, there have been but few pulmonary signs during convalescence.

For his kindness in directing the work and for valuable suggestions and criticism, the authors wish to express their sincere thanks to Dr. Torald Sollmann.

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[Reprint from the Cleveland Medical Journal, December, 1906]

A Clinical Study of 210 Cases of Acute Articular Rheumatism

BY JOHN PHILLIPS, M. D., CLEVELAND, OHIO

Since the opening of Lakeside Hospital in 1898, 210 cases of acute articular rheumatism have been admitted to the medical wards on the services of Drs Powell, Lowman, Upson and Cushing, and to these gentlemen I am indebted for the privilege of making this report. One out of every 27 admissions to the medical service have this disease, so that next to typhoid fever and pneumonia it is the most common of the infectious diseases with which we have to deal.

Etiology: Occupations which necessitate exposure to wet and cold predispose to rheumatic fever. Many of the patients were previously employed as laborers or as teamsters. In a considerable number, too, there was a history of working with wet clothing or with wet feet for several hours just before the onset of the attack.

In the cold damp weather of the spring months we see the largest number of cases. In January 18 cases of rheumatism were admitted to the Hospital, in February 10, in March 31, in April 31, in May 28, in June 22, in July 12, in August 7, in September 6, in October 12, in November 13, and in December 20. These figures differ very much from the statistics of the London Hospitals given by Dr Cheadle in Albutt's System of Medicine, in which the number of cases was smallest during the months of February, March, April, May and June, and greatest during September and October.

Eleven children under 12 years of age and 199 adults were affected. In 201 cases where the age was recorded, the number of patients at the different decades was as follows:

From 1 to 10 years	5 cases	2.49%
10 to 20 years	30 cases	14.92%
20 to 30 years	64 cases	31.84%
30 to 40 years	55 cases	27.36%
40 to 50 years	37 cases	18.41%
50 years upwards	10 cases	4.98%
	201 cases	100.00%

The above figures do not give one a correct estimate of the frequency with which the disease occurs at the different ages, for so often in children the joint symptoms are so slight that

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Read before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, November 2, 1906 they are entirely overlooked and therefore do not come under the care of a physician. Furthermore, many of the cases recorded under the last four groups have had previous attacks. However, the statistics emphasize the greater susceptibility to attack in youth and early adult life.

Adult males through their occupations are much more exposed to wet and cold, and, therefore, among them the disease is more prevalent. One hundred and forty-two males and 68 females were affected—a proportion, approximately, of 2.1 to 1. Until adult life the two sexes are about equally affected.

Heredity was a factor met with in seven percent of the patients. Cheadle holds that a hereditary predisposition is found in 20% of children afflicted with this illness. Hospital statistics are valueless in this respect, as many times the point of heredity is overlooked in taking the history, and frequently the laity call many things which are not acute rheumatic fever, rheumatism.

For some time acute articular rheumatism has been classified by writers among infectious diseases. In 1898 Triloubet described an organism, which he obtained from the joints of rheumatic cases, and he called it the micrococcus rheumaticus. His work was confirmed in 1899 by Wasserman, and also by Paine and Poynton, who obtained a similar organism in 18 cases. Further study by Beaton, Walker and Ryffel was made in 1903, and they succeeded in finding the organism in the heart's blood post-mortem, in the urine, and in the joint fluid. The organism is very small and is arranged in pairs and in short chains. Various observers have found that intravenous injections of cultures in rabbits cause fever, wasting, polyarthritis, endocarditis, pericarditis, septicemia and death. In this country Lewis and Longcope have had similar experimental results. Though this work has not been generally accepted, it gives promise that the definite cause of rheumatism will soon be discovered.

Symptoms: Acute articular rheumatism usually manifests itself rather abruptly after exposure to wet and cold. The patient complains of headache, chilliness, and irregular pains in the joints. Soon one or more joints become swollen, hot, tender on pressure, and so painful that the patient will cry out with the slightest jarring of the bed. The disease is as a rule fully developed in 24 hours. The temperature ranges from 100 to 104 degrees, depending on the severity of the illness and the number of joints involved. In none of the cases was hyperpyrexia present. The pulse volume is full and its rate increased to 100 or 120 beats per minute. The face is flushed, the tongue moist but coated with a heavy white fur, the patient is thirsty, the appetite is gone, and the bowels are constipated. The perspiration, as a rule, is very free and is highly acid in reaction. The blood in the acute stage shows a moderate leucocytosis ranging from 12,000 to 20,000. In one patient, where the disease was complicated by pneumonia and endocarditis, the white blood corpuscles numbered 60,000. With the drop in temperature and the subsidence of the acute inflammatory symptoms, the count of the white cells soon reaches normal. Rheumatism soon produces a marked anemia of the secondary type, the hemaglobin dropping occasionally to 45 or 50% and the red blood corpuscles sometimes numbering as low as 3,500,000. The urine is highly colored, scanty, of high specific gravity, and very acid in reaction. Albumin was present in amounts varying from the faintest trace to 1 gram to the litre in 142 cases, or 67%. In the uncomplicated cases, as a rule, only a faint trace was found. Where a greater amount than this was present, there was usually some cardiac lesion. Casts of the hyaline variety were noted in 64 cases or 30.4%. The albumin and casts disappear when convalescence is established.

The joints are swollen, hot, tender, and very painful on motion. There is a reddish tinge to the skin over the joints. Usually several are involved, the disease frequently subsiding in one as another is attacked. It has a tendency to affect the large joints, viz: knees, ankles and shoulders insteal of phalangeal or metacarpal. Effusion into the joint is not common. In the present series the frequency of the different joints affected was as follows: the left knee in 120 cases, right knee in 115 cases, left ankle in 98, right ankle in 80, left shoulder in 60, right shoulder in 57, left wrist in 53, right wrist in 51, left elbow in 46, right elbow in 39, left hip in 24, right hip in 20, the metacarpal and phalangeal joints of the hands in 32, the metatarsal and phalangeal joints of the feet in 20, the intervertebral and sacroiliac joints each in one case. In only 11 cases was the disease limited to one joint, a factor which is a great help in the differential diagnosis from the other joint affections. A number of times soreness and pain in the muscles accompanying the joint affection was noted.

Complications: Endocarditis is the most common complication of rheumatism. Undoubted valvular lesions were present in 63 cases or 30%. In only 28 of these was the endocarditis of recent origin. In 56 or 89% the mitral valve was involved, the aortic valve in 13 or 20.6%. Both aortic and mitral orifices were involved in 11 or 17.4%. The onset of this complication is accompanied by rise in temperature, rapid pulse, pain in the region of the heart, an increase in cardiac dulness, and the development of a systolic murmur at the apex of the heart. It occurs sometimes without such definite symptoms as these, so that the heart should be carefully examined daily. The younger the patient the more likely will endocarditis develop.

Pericarditis occurred in 10 cases, of which two were fatal. In four of these there was effusion into the pericardium of varying amounts. As a rule the effusion is small. The pericarditis manifests itself by the development of severe pain increased by pressure in the region of the sternum, by enlargement of the heart, and by the development of a friction rub in the second and third left intercostal spaces. If there is much effusion the rub may disappear. The area of cardiac dulness should be outlined with a dermatograph or with silver nitrate, so that any change in its area can be definitely determined.

It is difficult to say how frequently myocarditis is present in acute articular rheumatism. Usually it is coincident with an endo- or pericarditis. There were 31 cases in this series in which a systolic murmur was heard either at the apex or base of the heart, with no appreciable increase in the area of cardiac dulness and without the murmur, when present at the apex, being transmitted into the axilla. McCrae mentions the following possible causes for these doubtful murmurs, viz: (1) fever, (2) toxemia, (3) anemia, (4) myocarditis, (5) dilatation and (6) endocarditis. It is probable that in a number of these 31 cases there was some degeneration of the myocardium.

Pleurisy was noted in six cases, one of which was accompanied by effusion. The pleuritic rub is most commonly found in the fifth or sixth left interspace just outside the mammary line.

Pneumonia was present in two cases, one of which was fatal. Tonsilitis developed during the illness or was present before in 38 cases or 18.1%.

Nervous complications occurred in 13 cases. Of these four had delirium, in one of which it seemed to be associated with the giving of salicylates. In another case it assumed the type seen in delirium tremens, the patient having previously had attacks of this disease. Chorea was associated with the present or previous attacks of rheumatism in eight cases or 3.8%. These were all in children or in young adolescents. Serious meningitis was noted at autopsy in one fatal case. This patient, a man aged 33, three days after admission became delirious, his temperature rising to 103 and continuing between this point and 105 until death a week later. He had some retraction of the head and Kernig's sign. As the patient was a foreigner and could not make known when he was toxic from the salicylates, his meningitis may have been due to overdosing as he received 580 grains of sodium salicylate in 29 hours.

Subcutaneous fibroid nodules were observed in four patients —aged 6, 15, 12 and 29 years, respectively. They are most commonly found over the backs of the elbows, at the margins of the patella, and along the malleoli. However, they may occur anywhere over a bony surface as the superior curved line of the occipital bone, the spine of the scapula, the spines of the vertebra, or along the crest of the ilium. In a case in the Hospital at the present time there is a small nodule over the external condyle of the humerus, another in the axillary line over the sixth rib on the right side, and a third over the ensiform cartilage of the sternum. They may be very numerous, one of our cases having 70 in all. They vary in size, being usually as small as a pea, though they may be as large as a hazel nut, and they are freely movable. They are of prognostic importance in that they are generally associated with an endocarditis.

Miscellaneous complications are frequently seen. Erythema multiform was seen about the buttocks and upper part of the thighs in three cases. Rheumatic purpura, appearing as a bright red petechial eruption over both shins and accompanied by considerable tenderness, was noted in two cases. Urticaria occasionally develops and sudamina are very common because of the excessive perspiration. In one case complicated by pneumonia marked jaundice was present.

Diagnosis: The symptoms of acute articular rheumatism in the majority of cases are so typical that there is no difficulty in making a correct diagnosis. The suddenness of the onset, the flushed face, the rise in temperature, the acid perspiration, the polyarticular involvement, and the extreme helplessness of the patient make a very definite picture. Particular stress should be laid upon the fact that the use of salicylates in sufficient dosage to get toxic effects is of great diagnostic value. In our later work we have come to rely more and more on the observation that an arthritis which does not readily yield to the salicylate treatment is something other than acute articular rheumatism. The latter must be differentiated from gonorrheal arthritis, arthritis deformans, acute septic osteomyelitis, septic arthritis, gout and trichinosis.

Gonorrheal arthritis is distinguished by the appearance of the joint, the fixity of the pain, the tendency to affect the smaller joints as the metacarpal and metatarsal, the urethral discharge, which bacteriologically shows the gonococcus or history of previous acute urethritis, and the fact that as a rule only one joint is involved. In some cases, in which there is a gonorrheal septicemia, Thayer and Boggs have shown that it is possible to isolate the gonococcus from blood cultures. The possibility of gonorrheal involvement should always be kept in mind in case of doubtful arthritis.

Arthritis deformans in its early stages offers the most difficulty. In the proof of this fact I have been able to collect from our records five cases, originally diagnosed as acute articular rheumatism, who have been subsequently readmitted to the hospital with unmistakable signs of arthritis deformans. These cases, however, do not have cardiac complications, the temperature as a rule is not so high as in rheumatism, the pain in the joints is not so severe, and unusual joints, as the intervertebral, the sternoclavicular, and the temporomaxillary, are involved. Another important point is that the early cases of arthritis deformans do not yield to the salicylate treatment.

Acute septic osteomyelitis may be distinguished by the fact that the illness is more profound, the leucocytosis higher, and the disease attacks the epiphysis of the bone instead of the joint itself.

Septic arthritis in children at times offers great difficulty in differential diagnosis. In these cases the temperature is higher than in rheumatism, the prostration is more marked, and generally only one joint is involved. Recently a child three years old was admitted to the children's ward with the diagnosis of acute articular rheumatism. The child looked very ill, its temperature was 103 degrees, the prostration was marked and the right elbow was swollen, hot, very red and painful. The next day an incision was made over the joint and considerable pus, which gave pure cultures of the pneumococcus, escaped.

In gout, the age, sex, occupation and general habits of living are all important in making the diagnosis. It generally affects the second joint of the great toe, which is seldom attacked in rheumatism. In one case the polyarticular manifestations of gout were mistaken for rheumatism, and when he was readmitted a few months later, tophi were found in his ears.

One seldom thinks of trichinosis in connection with the differential diagnosis of rheumatism from other conditions. In the past year, however, two undoubted cases of trichinosis were admitted to the medical wards, with a diagnosis of rheumatism having been made by outside physicians. In these cases the presence of marked eosinophilia, the tenderness limited to the muscles and not affecting the joints, and the finding of the trichinæ themselves, by snipping out a piece of the affected muscle, will clear up the diagnosis.

Rheumatism in children differs materially from the adult type. Often there are no joint symptoms, an endocarditis being the first warning that the child has the disease. In taking the history of a child with endocarditis, the physician should always inquire carefully from the mother whether there have been "growing pains," as often this is the only manifestation of rheumatism seen in children.

It is difficult to say what will be the course and prognosis of a given case of rheumatism. If uncomplicated, under active treatment the joint symptoms will disappear in one to three days. If the heart is damaged the course is prolonged and it may leave the patient a confirmed invalid. Six or 2.8% of this series ended fatally. Hospital cases, however, do not come under treatment until late in the disease.

Treatment: The patient, clothed in a flannel nightgown, should be kept at rest in a comfortable bed and should lie preferably between blankets. Abundant drinking of water is necessary to favor elimination and to make up for the fluid lost through free perspiration. Instead of plain water, cream of tartar water may be substituted. The bowels should be opened freely by the administration of calomel followed by a saline and afterwards kept moving regularly by cascara. Where the perspiration is free, the patient can be made comfortable by sponging his body with water to which sodium bicarbonate has been added. The diet at first should consist of milk, although if the latter is not well borne, there is no objection to giving soups, animal broths, rice or tapioca. Because of the great tendency to anemia, the patient should be placed on a liberal diet as soon as the temperature is normal.

Much has been claimed for the alkaline treatment of rheumatism, that it shortens the course, and that it prevents the development of endocarditis by depressing the circulation. Though the alkalis may be useful adjuncts to treatment no drugs give such marked beneficial results as the salicylates. Indeed we have come to look upon them as a specific for this disease. The best form is the sodium salicylate from the true oil of wintergreen. If this disagrees with the stomach, the oil of wintergreen itself, aspirin or salicin may be tried. The hospital routine is to give 20 grains of the sodium salicylate every hour until the patient is toxic, the total amount not to exceed 200 grains. If the patient is then not toxic and the disease has not yielded to treatment, we continue giving the salicylate, watching closely the effect of each dose, until in some cases as much as 300 grains have been taken. There is less likelihood of disturbance of the stomach if the salicylates are given well diluted and in combination with sodium bicarbonate. It is gratifying, indeed, to see the remarkable transformation in the patient. Patients, admitted in the afternoon with a temperature of 103 degrees and joints so painful that they scream with pain if the bed is touched, next morning have a normal temperature and move their joints freely, the pain, tenderness, and swelling having all disappeared. Often, cases, who without benefit have been treated outside the hospital with small doses of salicylates, rapidly clear up when the drug is pushed to its toxic limit. Seldom is the stomach disturbed. The toxic symptoms noted are ringing in the ears and deafness. For a full consideration of the therapeutic and diagnostic value of massive doses of the salicylates in acute articular rheumatism, the reader is referred to an article by Dr Clarke in *American Journal of Medical Sciences,* September, 1906.

Local treatment of the joints is of secondary importance, though it is very comforting in the acute stage. Oil of wintergreen should be painted on the joints and they should be wrapped in thick cotton wadding. Greater relief is sometimes given by the application of hot stupes of lead and opium, or by the application of menthol and oil of wintergreen ointment.

After the acute symptoms have subsided the local applications are discontinued and 15 to 20 grains of sodium salicylate are given three times a day. To ward off anemia, iron should be prescribed early. The patient should be kept in the recumbent posture for three weeks to avoid cardiac complications. This is especially difficult with the salicylate treatment as the patient feels so well in two or three days that he often demands to be allowed up.

In acute endocarditis and pericarditis an ice-bag should be applied to the chest. The damage to the valves in the former complication may be lessened by prolonged rest in bed and by the use of small doses of potassium iodid in the late stage. If the effusion in pericarditis becomes large, paracentesis is indicated. The use of blisters over the sternum hastens the absorption of the effusion.

In children, especially, subsequent attacks may be prevented by giving sodium salicylate in small doses for one week out of each month, continuing this for at least a year. If the child has endocarditis with enlarged heart, a prolonged stay of at least six months in bed is advisable. Plenty of fresh air is needed and the patient should be kept amused with his toys and books, care being taken to avoid excitement. One year ago a child six years old was admitted to the hospital, suffering from rheumatism, with chorea, subcutaneous fibroid nodules, and an enlarged heart, the left border of which reached nearly to the anterior axillary line. He was kept in bed six months and treated as outlined above. At the end of that time, the chorea was well, the subcutaneous fibroid nodules had disappeared, and the left border of his heart was just outside of the mammary line.

In conclusion I wish to express my indebtedness to Dr Edward F. Cushing for many valuable suggestions in the preparation of this paper.

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Treatment of Typhoid Fever

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There is no subject of greater interest to the practitioner of medicine than the treatment of typhoid fever. This interest comes, on the one hand from the fact that this disease is met with in hospitals, and in private practice, at all seasons of the year, and, on the other hand the course is so prolonged and so many complications may arise, that the physician must always be on his guard to keep his patient comfortable and restore him to health. The treatment which I shall outline is that which has been carried out on 1070 cases of typhoid, admitted to Lakeside Hospital on the services of the visiting physicians: Drs Powell, Lowman, Upson and Cushing. The mortality in these cases was 7.9%.

Prophylaxis: Since the sources of infection with the typhoid bacilli are so well known, we should use every precaution to prevent their entrance into the body. The usual source is from a bad water supply. In the city of Cleveland in 1903 there was a severe epidemic of typhoid fever, due to the drinking water being contaminated by the sewage passing out into Lake Erie close to the intake pipe, and 367 cases were treated in our hospital wards. With the building of a new intake pipe farther out into the lake, the disease became less prevalent, and in 1905 we had only 71 cases and quite a number of these came from outside the city. If one suspects that his water supply is infected, it should either be boiled or

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Read at a meeting of the Huron County Medical Society, at Norwalk, July 12, 1960 filtered before using. One should bear in mind, however, that a poor filter may in itself be a source of great danger. Another source of danger is from milk, if the cans, previous to their use, have been washed with water infected with typhoid bacilli. Raw oysters are often dangerous. Fresh vegetables should always be washed thoroughly with water that has been boiled, as they may be contaminated from the fertilizer used to promote their growth. In a case recently in our wards, that was the only source of infection that we could find. I would like, especially, to emphasize the danger of flies spreading the disease. A fly may light one moment on a typhoid stool, and in another moment be in a glass of milk, directly carrying the infection. The hospital ward or sick room should therefore be well screened.

A typhoid patient himself may readily spread the disease, especially if the proper care is not taken in the disposal of urine and feces. These should be passed into a bed-pan containing a solution of carbolic acid 1-20, and afterwards all solid particles should be broken up and allowed to remain thoroughly covered with the disinfectant for two hours. In hospitals a specially constructed steam sterilizer, connected with the sewer pipe, is preferable for the disinfection of the excreta. The danger from the urine may be greatly lessened by the use of urotropin in convalescence. All bed and personal linen should be carbolized immediately on removal. The patient should be provided with separate dishes, thermometer, and bed-pan. If there are several typhoid patients in a ward, a separate bed-pan for each is very important to avoid the spread of boils, a frequent complication in convalescence. Nurses and orderlies after attending to the patient should thoroughly disinfect their hands, and especially before eating. Where many typhoid patients have to be cared for, this is apt to set up a dermatitis of the hands, a difficulty which may be obviated by wearing loose-fitting rubber gloves. These are used routinely on our medical wards in handling the bed-pans used by typhoid patients, and they absolutely protect the nurse from carrying the infection to other patients or from becoming infected herself.

GENERAL MANAGEMENT OF PATIENT

Careful nursing is one of the most essential things in the treatment of typhoid, and in no other disease is attention to details so important. The room should be well ventilated.

its temperature not higher than 65 degrees, and, if possible, in warm weather the patient should be out of doors part of the time during the day. The bed should be high enough to facilitate the easy care of the patient. The mattress should not be too hard. Over it should be placed a rubber sheet, and next a sheet of fine texture, so that it can be kept perfectly smooth. The covering of the patient should be light, a sheet and spread being all that is necessary. If the patient feels very chilly, a blanket may be put on the bed, but this should be removed as soon as he is warmer. One hair pillow is all that should be used. Special attention should be paid to the care of the patient's back. The sheet should be kept perfectly smooth, the patient encouraged to lie on his side a part of the time, and the skin kept clean, especially about the sacral and anal regions. The back should be rubbed twice a day with alcohol and afterwards dusted with talcum powder. If the urine and feces are passed involuntarily, the soiled linen should be removed at once so as to keep the patient as dry as possible. Bowel movements should be passed in the recumbent posture. Where there is careful nursing bed sores are not common. In our series of 1070 cases they were present only in 10 cases and these were patients who had either involuntary micturition and defecation, or in cases of severe hemorrhage, in which the patient had to be disturbed as little as possible. In some, too, the bed sores were present on admission to the hospital.

The care of the mouth is a very important part of typhoid nursing. Where large quantities of water are taken this is an easy matter. Twice daily the nurse should wrap the index finger of her right hand with lint, dip it in the typhoid mouth-wash and scrub the tongue thoroughly, holding it out with the other hand. The cheeks and teeth should also be cleaned thoroughly. The mouth-wash used consists of the juice of two lemons, boracic acid ʒ iv, glycerine ℥ i, water qs. ad Oi. After each feeding the mouth should be sprayed with 10% boracic acid solution. I cannot too strongly recommend the use of the atomizer in cleaning the mouth and throat.

Close attention should be given to the care of the bowels, since the disease shows its most marked manifestation here. They should be kept at rest as much as possible to assist in the healing of the ulcers. Early in the disease an initial cathartic of calomel should be given. If constipation is present, a soap suds enema should be given every other day. If there is a tendency to fecal impaction, which is not very uncommon in the fourth week of the disease, it is better to give a daily enema of olive oil ℥ iii, glycerine ℥ i. Often in children, and occasionally in adults, a rectal examination is necessary to remove the impacted feces. After the temperature has been normal for four or five days in ordinary cases, or in long protracted cases with slight fever and marked constipation, it is well to substitute a cathartic for the enemata, using either castor oil or compound licorice powder, and afterwards keeping the bowels moving regularly by the use of cascara. Indeed, constipation is the most common cause of rise of temperature during convalescence. Only about 10% of our cases had diarrhoea. This may be treated by bismuth, or by the use of the lead and opium pill. An enema of starch and laudanum is often of great assistance.

Water should be given freely. The routine in the hospital is to give four ounces of water every 15 minutes during the day, and whenever the patient is awake at night. When given freely in this way, and in small quantities, the water produces little or no gastric disturbance, and no discomfort to the patients. We have very little difficulty in getting our patients to take the water, as they soon realize how much more comfortable it makes them. The excretion of urine will reach, on an average, after three or four days, 200 ounces, and in one case 512 ounces for the 24 hours. The urine is clear, of low specific gravity, and is tolerated well by the bladder, for in the last 200 cases retention of urine has occurred only twice. In only one case have the kidneys refused to excrete readily. The temperature is lower, the patient complains less of headache and are less toxic, delirium and sleeplessness being very uncommon. The mouth and tongue are clean, so that such complications as parotitis and otitis media are infrequent. It is very rare that the stomach is disturbed, and distension is not increased. As the patient approaches convalescence water is given at longer intervals or only as the patient desires it. A full consideration of copious water drinking in typhoid is found in an article in the *American Journal of Medical Science,* 1905, by Drs Cushing and Clarke.

The problem of feeding typoid fever patients is important, as the disease runs a long course and causes great emaciation. The diet should be nutritious, and yet yield very little residue to irritate the inflamed bowel. Milk is the ideal diet, and the object of giving other liquids with it should be to encourage the patient to take milk better. The latter should be as pure as possible, otherwise it will cause diarrhoea and distension. Our routine is to give six to eight ounces of milk alternating with albumen water. The patient is fed every two hours during the day and every four hours during the night. In some cases in which the stomach is irritable, it is necessary to dilute the milk with lime water or partially peptonize it. If milk is disliked it will be taken more readily if flavored with tea or coffee. Sometimes a good substitute is koumyss or buttermilk. The patient is kept on this diet until convalescence is established. Then we give more freely other liquids as beef broth, cocoa, chicken broth, strained soups (except potato, tomato and bean soups), and often add custard and junket.

The time when soft diet is started depends on the condition of the patient. In cases in which the disease has run a long course, the emaciation is extreme, and the patient hungry, we feed several days before the temperature is normal. We are guided also by the size of the spleen and the condition of the tongue. A spleen steadily decreasing in size, a clean tongue, and a condition of hunger, are all indications for early feeding. In our earlier work in which we delayed feeding until several days after the temperature was normal, we saw more cases with emaciation, more with subnormal temperature, and more with boils, and other complications, due to a condition of lowered vitality. Hemorrhage and perforation do not occur more frequently with earlier feeding. Indeed our statistics show that they are less frequent, although one is not safe in drawing conclusions from the latter alone. We keep our patients on typhoid soft diet No. I for four days. It is as follows:-

1st day—Dinner. A small piece of thoroughly softened milk-toast without crust. Liquids every two hours as before.

2nd day—Breakfast—soft toast. Dinner—soft toast and soft boiled or poached eggs. Liquids every two hours.

3rd day—Breakfast—soft toast and egg. Dinner—soft toast, egg and custard or junket. Supper—soft toast. Liquids every two hours.

4th day—same as third day with the addition of well cooked rice.

Following this we increase the diet to typhoid soft No. II, which is the same as the above diet, with the gradual addition of the following: cereal, crackers, scraped beef, creamed chicken, bread and butter, and milk pudding. During this time it is very necessary that milk be given between meals and in the evening, so that small amounts of solid food at a feeding will satisfy the patient. In the course of five days, if convalescence is uninterrupted, we give typhoid convalescent diet, which consists of the following:

6:30 A. M.	Cereal, toast, egg, chop, milk ℥ ii, coffee ℥ iv.
9 A. M.	Milk ℥vi, and crackers.
11:30 A. M.	Chicken, steak, rare roast beef, chop or fish, potatoes, baked custard, bread with crusts, soup and milk.
2 P. M.	Milk ℥ vi.
4:30 P. M.	Toast, egg, creamed chicken, stewed fruit, broth and tea.
8 P. M.	Milk ℥ vi.

The above diets are given merely as a guide. They should be varied to suit the needs of each case.

The efficiency of the bath treatment of typhoid fever has for a long time been universally recognized. Tub baths at 90 degrees should be given every three hours during the day, and every four hours during the night, when the rectal temperature is above 102.5 degrees. The duration of the bath is 15 minutes, and while in it the patient should be rubbed vigorously by two assistants. The head should be supported on a rubber cushion and cloths wrung out of ice water kept constantly applied to the forehead. The temperature is taken before and one half hour after the bath. Since the introduction of the warmer baths, the patients do not fear them, there is less shock, and cyanosis is infrequent after them. If cyanosis does occur and the extremities are cold, relief will follow a hot mustard foot bath, and the administration of half an ounce of whiskey. The drop of temperature is almost as marked with the colder baths, and the general discomfort much less. Intestinal hemorrhage and perforation occur less frequently, because there is less constriction of the peripheral, and, therefore, less congestion of the internal vessels. Often after the temperature is below 102.5 degrees, it is well to give a bath every evening for the general comfort of the patient, and for the quieting effect in producing sleep. The giving of tub baths is contraindicated in the case of phlebitis, intestinal hemorrhage, and in conditions of extreme weakness. If they cannot be conveniently given, a sponge bath at 90 degrees for 15 minutes may be substituted. Most patients prefer the tub to the sponge baths, though good results may be obtained with the latter.

TREATMENT OF SPECIAL SYMPTOMS

An ordinary uncomplicated case of typhoid fever can be carried through its course without the administration of drugs, but often special symptoms or complications arise, in which they are a great help if not a necessity.

Headache is often very troublesome in the earlier stages of the disease. In the milder forms an ice-cap is all that is necessary. Another great aid is the giving of water freely to assist in the rapid elimination of toxines from the body. If severe and persistent, the tincture of ipecacuanha and opium mx repeated every half hour for three doses gives great relief. Occasionally the use of a small dose of phenacetin, guarded by caffein, is very effectual, though it should not be repeated because of its depressant effect. A few cases can be relieved only by a hypodermic injection of morphia.

Vomiting occasionally occurs and is very distressing. If due to any particular article of food, this should be stopped, though it is wise in most cases to stop all food until nausea ceases. The water as a rule does not have to be discontinued, but it should not be given quite so frequently. A hot water bottle, a mustard plaster, or an electric pad to the epigastrium, gives marked relief. Sodium bicarbonate, bismuth subnitrate and dilute hydrocyanic acid are of great assistance. We often prescribe tiny doses of creosote and carbolic acid with good results. After nausea ceases, the return to the ordinary typhoid diet should be gradual, beginning first with peptonized milk, then milk diluted with water, gradually increasing the strength and quantity.

Abdominal distension is a dangerous symptom, not only because of its interference with the free action of the heart and lungs by its pressure upward on the diaphragm, but also because of the increased liability to perforation and intestinal hemorrhage. Mild cases are usually quickly relieved by turpentine stupes to the abdomen and by giving a high enema of magnesium sulphate ℥ ii, glycerine ℥ ii, turpentine ℥ ss, one egg and water to make a pint. In a few cases the most effectual enema consisted of olive oil ℥ iv, turpentine ℥ ss,and emulsion of asafoetida qs ad ℥ xiv. Turpentine should be tried internally in cases in which the distension persists. Some cases that will not yield to the hot stupes are greatly benefited by the ice coil. The use of the rectal tube we have found of assistance only in a small number of cases. Another good measure is to touch the abdominal wall lightly with the paquelin cautery. One should not forget, however, that part of the distension may be due to a stomach dilated with gas. In these cases the food should be stopped and sodium bicarbonate gr. xx and spirits of peppermint mxx in one-half a glass of hot water given. This is usually followed by the belching of large quantities of gas. If this does not occur a stomach tube should be passed.

Cholecystitis was present in 12 cases. In mild cases it usually subsides after a few days with the application of an ice-bag. If the gall-bladder becomes greatly distended, or pus accumulates in it, an operation is necessary.

Intestinal hemorrhage occurred in 63 cases of our series or 5.88%. In a hemorrhage of moderate amount the treatment is to keep the patient as quiet as possible, avoiding unnecessary moving in bed, such as turning or assisting himself in any way. The baths, stimulant medicines, food and his regular enemata should be discontinued. Water may still be given in moderate quantities. An ice-bag or, better, an ice coil, should be kept constantly applied to the abdomen. To quiet the patient and to lessen the peristaltic movement of the intestines morphia should be given freely. It has one disadvantage, however, viz., that it may obscure the symptoms of perforation, should it subsequently occur. To increase the coagulability of the blood, calcium chloride gr. xx every three hours is of great assistance. Another aid in this direction is the subcutaneous injection of 2% gelatin solution. In case of severe intestinal hemorrhage, the foot of the bed should be elevated, the heart supported by strychnia and digitalin hypodermically, subcutaneous or intravenous injections of normal saline solution given, as well as by carrying out the measures referred to above. The bowels should not be moved for four days. Then an oil enema should be given and retained for a couple of hours, to be followed at the end of that time by a soap and water enema. One half hour previous to the giving of the latter, m. xv, of the adrenalin chlorid solution (1-1000) should be given, to relax the bowel wall and permit the easier passage of the stool. Sixteen of our cases of hemorrhage were fatal.

Perforation of the intestine was found in 29 of our cases or 2.7%. Medicinal treatment has nothing to offer in these cases. The doctor and the nurse should be on the lookout and every case of typhoid fever complaining of abdominal pain, should be thoroughly examined and watched, so that the diagnosis can be established early. Operation in these cases saves from 25 to 30% and the earlier the diagnosis is made, the greater the number of cases saved. If the diagnosis is in doubt, I think an exploratory operation under cocain is justifiable as there is little shock connected with it.

Severe cardiac disturbance is not common in typhoid fever, if the patient is kept flat in bed until 10 days at least after the temperature is normal, and judicious stimulation used if the first sound of the heart loses its booming character. When this is first noticed and the pulse is increasing in rapidity, or is irregular, alcohol in moderate doses or strychnia should be given. For the severer forms of cardiac trouble digitalis should be employed. If rapid stimulation is needed, hypodermic injections of camphor and ether should be used.

Phlebitis occured in 42 cases or 3.9%. It may occur at any time during the course of the disease. Frequently it appears after the patient has begun to walk, from over-exertion. It usually occurs in the femoral vein of the leg. The limb should be kept at rest and elevated on two pillows, the weight of the bed-clothes being supported by a cradle. An ice bag should be kept constantly applied over the inflamed area. The baths should be discontinued and any undue manipulation of the limbs avoided. If an abscess forms, an incision should be made, the pus evacuated, and drainage established.

Otitis media was present in 31 cases or 2.89%. Though usually accompanied by pain and rise in temperature, its onset, however, may be so insidious, that the first indication is a serous discharge from the ear. It occurs less frequently in cases that take water freely. When diagnosed early a paracentesis of the ear drum should be made as soon as it shows signs of bulging. If this discharge remains serous, the ear should be carefully swabbed out frequently with sterile cotton on a probe, and afterwards protected by pledgets of sterile cotton placed loosely in the external auditory meatus. If the discharge becomes purulent, in addition to this, the ear may be swabbed out with hydrogen peroxid or 50% menthoxol. If the otitis media becomes chronic, the use of a solution of boric acid and alcohol assists greatly in the healing process. Syringing the ear should not be resorted to, unless there is great destruction of the drum and a very abundant discharge.

Bronchitis occurs frequently at the onset of typhoid and sometimes in the later stages. Pneumonia, too, is occasionally observed. These complications as a rule require no special treatment and they do not prohibit the use of tub baths.

Tender toes often are seen in the third and fourth week of the disease. If the bed cloths are tucked in too tightly at the foot of the bed so as to produce pressure on the toes, this complication is more frequently seen. The bed clothes should be supported on a cradle and the toes painted with equal parts of alcohol and iodin. Sometimes menthol and oil of wintergreen ointment gives greater relief than the latter.

Cystitis occurred in nine cases and pyelitis in two cases in our series. Urotropin gr. x three times a day should be used both as a prophylactic and curative measure. We give it routinely during convalescence. As a rule these cases subside readily without any further treatment.

Many minor complications occur during the course of the disease which should be treated on general principles.

At no period of the disease is there such satisfaction to the doctor and nurse as in the period of convalescence, when we see the patient very hungry, gaining one pound per day, and his strength rapidly returning. A second pillow should be given to the patient on the eighth day of normal temperature, and a bed rest on the tenth day. He is given the bed rest one-half hour forenoon and afternoon of the first day, doubling the time on each succeeding day for three days. His pulse should be watched carefully and if it becomes very rapid or irregular or if he feels faint, he should be changed to the recumbent position at once. On the fourteenth day he is given the wheel chair one half hour forenoon and afternoon, doubling the time for three succeeding days. On the eighteenth day walking is allowed, care being taken that the patient walks only a few steps at first, and gradually increasing the distance walked day by day. If the patient walks too freely, phlebitis is apt to occur. This routine should be varied for individual cases. Children should often be allowed up early, otherwise they may develop bed fever. When walking is allowed, care must be taken that the patient wears shoes and not slippers, so as to prevent the development of flat foot, as the ligaments of the plantar arch become much relaxed during the prolonged stay in bed. An iron and strychnin tonic should be given during the convalescence. After leaving the hospital the patient should take a long vacation, as it takes the physical and mental powers a long time to regain their activity. All indigestible food should be avoided. I would emphasize too the importance of examining the lungs frequently during convalescence, as the onset of tuberculosis is often very insidious.

In conclusion I wish to thank Dr Edward F. Cushing for many valuable suggestions in the preparation of this paper.

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Vincent's Angina

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During the past few years much has been written, especially in the German and French journals, about a somewhat rare form of ulcero-membranous, and at times membranous inflammation of the tonsils and pharynx in which two forms of micro-organisms can be isolated in coverslip preparation, one a fusiform bacillus, the other a spirochaeta. These when properly looked for are present in almost pure culture.

The disease is of especial interest and importance because it is frequently confounded with diphtheria and syphilis.

In view of the fact that Vincent first gave to the medical profession the most accurate and complete description of the condition from both a clinical and pathological standpoint it has been called after him Vincent's Angina. There seems to be some doubt as regards the justice of this from the standpoint of priority of discovery, for H. C. Plaut in 1894, two years before Vincent's earliest paper, in an article entitled "Studies Regarding the Bacteriological Diagnosis of Diphtheria and the Anginas" reports the case of a little girl four years of age, sent in with the diagnosis of severe septic diphtheria in December, 1892. Examination showed many carious teeth and membranous deposits upon both inner surfaces of markedly swollen tonsils and upon the left side of the uvula. Considerable inflammation of the gums was present. There was moderate swelling of the glands of the neck. Microscopic examination of the membrane showed what Plaut called Millers' spirochaetae and Millers' bacilli in large numbers. Diphtheria bacilli were neither demonstrable by cultures or animal experiments. Upon blood serum only streptococci developed. On the third day the temperature was normal, the membrane gone and only the slightest reddening of the throat remained. Seven weeks later the seven-year-old son of the foster parents of this child became ill with the same disease and the same micro-organisms were found, but could not be cultivated. The child became well

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Read before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, October 6, 1905 in four days time. Plaut mentions three other cases of similar type and gives the symptom complex as being the sudden onset, the marked fetor of the breath, the high temperature and tough membrane, with the later rapid disappearance of all symptoms. He was evidently dealing with mixed infection.

Plaut gives Miller the credit of discovering the micro-organisms in 1883, and speaks of Miller's bacillus as being larger than diphtheria bacilli, pointed at the ends and always associated with spirochaetae.

He states that Miller found these micro-organisms in numbers increased beyond normal about the edge of badly inflamed gums and mentions a case cited by Miller where Verneuil and Clado found them in an abscess of the finger tip caused by laceration upon artificial teeth and in another instance in an abscess of the submaxillary gland.

In 1896, H. Vincent described the same bacteriological picture in cases of hospital gangrene seen in Africa.

In 1898, Vincent and Bernheim slightly later reported the same micro-organisms in practically pure growth in ulcero-membranous lesions of the tonsil of peculiar type.

Since then numerous contributions have been made to the literature and our knowledge of the disease picture and symptom complex further enlightened.

In this country, Sobel and Hermann, in December, 1901, reported 12 cases at the Good Samaritan Dispensary, New York.

Mayer reported a case in 1902; Fisher, two cases in 1903; Berkley, in 1903, wrote of the condition and recently reported a series of 29 cases met with during the past three years. Vincent gives the literature to date in the May Lancet, 1905, in a brief communication.

From a perusal of the literature the following facts have been gleaned. This type of inflammation of the tonsils is comparatively rare in Europe and America, generally overlooked and confounded with diphtheritic and syphilitic ulceration but easily recognized by microscopical and bacteriological investigation.

The disease is especially frequent in childhood at the time of the second dentition, rare after 35 years of age and comprises 2.26% of all types of anginas in adults.

Poor nutrition, tobacco, and occupation are factors of etiological importance. Thus students of medicine who make dissections and orderlies working in anatomical laboratories are said to be more prone to infection. Both sexes seem to be equally liable to the disease.

The site of election in the immense majority of cases is the tonsil, usually one, rarely both. In Berkley's series the right tonsil was involved 14 times, the left 7 times and both once. In Sobel and Hermann's series the right side was involved 6 times, the left 4 times, and both twice. Four of Vincent's 100 cases had involvement of both tonsils.

Several instances are given in the literature testifying to the communicability of the disease though it must be rare. Plaut, Berkley, Sobel and Hermann, Auchea and Baron have all reported cases in which the communicability of the disease would seem to be established. Sobel and Hermann mention the case of two sisters who had the disease simultaneously and three weeks later a third sister was affected.

Vincent divides the disease into classes; the ulcero-membranous, and the diphtheroid, the former, the common variety, the latter, present in 2 out of 100 cases.

In the first class of cases the process is apt to begin in the upper angle of the tonsil as a greenish or dirty gray membranous-like area of necrosis, which looks not unlike diphtheria at times and which bleeds easily upon contact with food or a swab.

Soon a definite loss of tissue is made manifest and upon examination one finds a more or less deep crater-like excavation whose surface is covered with necrotic tissue, fibrinous exudate, pus and saliva. This superficial covering may hide the destructive nature of the process unless one is careful. One or both tonsils, and in two cases reported by Bandi the uvula, may be involved in the destructive process to such an extent that there is little tissue left.

The symptoms are those of a subacute sore throat in a case of average intensity, though the clinical picture may be complicated by mixed infection. Headache, general malaise, chilly sensations and fever are present, though the temperature rarely is higher than 102.5°. The breath is foul; there may be considerable tenderness of the throat, especially upon swallowing, and often there is considerable enlargement of the submaxillary glands.

In a case of average severity the symptoms abate in from three to four days time though the local appearance of the throat may persist for a variable length of time.

The duration varies from a few days to six weeks.

The prognosis is good, depending for the most part upon whether a mixed infection is present or not, and if so upon the nature of it.

The disease may be associated with diphtheria, syphilis, and the ordinary streptococcus and staphylococcus infections of the throat.

In the diphtheroid form of this disease Vincent states that there is no ulceration but simply a membranous inflammation in which only the fusiform bacilli can be isolated.

The diagnosis of Vincent's angina is made by careful microscopical and bacteriological examination of scrapings taken from the floor of the ulcerating surface. If swabs are made in the ordinary way the condition is apt to be overlooked owing to the fact that a great variety of micro-organisms are present in the superficial necrotic material and comparatively few fusiform bacilli and spirochaetae. One should take an öse made of stiff platinum wire and, after removing the superficial debris, scrape the floor of the ulcer and make cover slip preparations from the scrapings. These should then be dried in air and may be fixed and stained in various ways. Dilute carbol fuchsin, aqueous solutions of thionin, Löffler's methylene blue, Wright's stain and Giemsa's stain all give excellent results.

Smears stained by any of these methods show varying numbers of fusiform bacilli and spirochaetae. The fusiform bacilli vary in length from 6 to 14 microns and in width from 1 to 2 microns. They are generally straight, though they may be curved and have pointed extremities. The centres are swollen and not infrequently there is a globular swelling at the centre which bulges the cell wall to a marked degree. At times these micro-organisms appear as diplo-bacilli. No definite spore formation has been made out. Gram's stain gives variable results though usually decolorizing. In fresh preparations the bacilli usually are motile and may be very actively so. The spirochaetae are of variable length, one-half to one-third the thickness of the bacilli and showing from two to five and occasionally more twists.

At times these twists are not very definite and the micro-organism has more the appearance of a spirillum than of a spirochaeta but again very definite corkscrew twists are present. These spirochaetae are likewise actively motile and stain with the same stains as do the fusiform bacilli though to a less degree. They decolorize by Gram's method of staining.

Cultural experiments have been rather unsatisfactory. The micro-organisms can be recovered in mixed culture from abscesses produced by inoculating mice and guinea pigs with material scraped from the base of the ulcer but the animals recover unless killed by contaminating streptococci, pneumococci or staphylococci. Cultures in artificial media have likewise been dissappointing. The micro-organisms can be found in mixed cultures for several days and then disappear. Mixtures of bouillon and various body fluids have given the best results.

It is evident from these results that very little is known about the life history of the micro-organisms. Some observers consider them different stages of the same organism and others that the relationship is one of symbiosis.

Fusiform bacilli and spirochaetae have been described in other conditions than those of the tonsils.

Vincent states that they were present in small numbers in 22 out of 27 normal throats examined.

They have been found in the following conditions: ulcero membranous stomatitis; alveolar abscess; pyorrhoea alveolaris; ulcero-membranous inflammation of the tongue; purulent periostitis of the right upper jaw with phlegmon of the temporal muscle, purulent meningitis and secondary gangrene of the lung; abscess of the antrum of Highmore; peri-laryngeal abscess; abscess of the finger; abscess of the thigh, lungs and brain; empyema; pus upon the stump of tonsils after tonsillotomy; in the mucus from a case of dysentery.

The treatment consists in the local application of tincture of iodine, silver nitrate or some other antiseptic solution in conjunction with frequent gargles, the abstaining from solid food while the throat is sensitive and the observance of a moderate degree of quarentine until the throat clears up.

Inasmuch as the condition has been found associated with diphtheria in rare cases, cultures should always be taken in order to rule out the possibility of a coexisting diphtheria. If there is any question as regards the diagnosis, antitoxine should of course be given and in sufficient dosage to control diphtheria if present, though the presence of these micro-organisms in practically pure culture is against the probability of diphtheria. The fusiform bacilli differ from diphtheria in their greater size, their motility, their poor staining by Gram's method, their morphology and in their cultural properties.

Syphilitic ulceration may simulate this condition closely though the presence of large numbers of these micro-organisms would be against the probability of a coexisting syphilis. With Giemsa's stain these spirochaetae stain blue and rapidly while those of syphilis even of they were present (though they have not been found in tertiary lesions) would stain with difficulty and would take the pink stain. The history would also help out in the differential diagnosis.

In thrush the presence of the oidium albicans, the less tendancy to ulceration and the more white and spreading character of the membrane would serve to differentiate the two conditions.

The ordinary staphylococcus and streptococcus inflammations of the throat differ from Vincent's angina in the usually more severe constitutional disturbances, in the former the absence of the fusiform bacilli and spirochaetae; the greater tendency to ulcerate in Vincent's angina.

Points which have been brought forward as evidence in favor of fusiform bacilli and spirochoetaea being of etiological importance in Vincent's angina are these; their uniform presence in large numbers and practically pure culture; their gradual disappearance during the process of healing; the presence of so few other micro-organisms in the neighborhood of the active process; finally the transmissability of the disease in certain cases reported.

As regards the four cases which I wish to report I will merely say that the bacteriological picture is perfectly characteristic in all of them, fusiform bacilli and spirochaetae being present in large numbers and in practically pure culture in the coverslip preparations made. This will be evident to all when you look through the microscope. The right tonsil was involved alone in three of the cases and both tonsils in the fourth case. There was a loss of tonsillar tissue comprising about one third of both tonsils in this case and the disease recurred one month and a half after no more micro-organisms could be discovered in the floor of the healed ulcers. All of the cases were males and two of these physicians one of whom is a pathologist. The subjective symptoms were about as described by Vincent and cultural experiments so far, as also animal inoculations, have resulted negatively. Otherwise there are no features of particular interest.

I have seen spirochaetae and fusiform bacilli morphologically identical with these twice in mixed culture in pus from gangrene of the lung and a few quite often in the feces especially where there was a tendency to diarrhoea. In a stool examined recently where amoebae dysenteriae were present I found large numbers of spirochaetae many of which were very actively motile. There were also a few bacilli of a morphology suggestive of fusiform bacilli and quite a number of trichomonads.

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THE FUNCTION OF THE ACCESSORY CAVITIES OF THE NOSE.*

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The functions of most of the organs of the body are so well known that, with our present knowledge, these functions seem almost self-evident. There are, however, some organs which are apparently functionless and are usually considered vestigial or rudimentary. They were formerly of greater physiologic importance, but in the course of generations, in consequence of adaptation of the body to special conditions of life, they have been subjected to reduction or degeneration and now remain simply as vestiges. Their presence can be explained only by the theory of selection, and in this connection, two important factors must be considered, namely, heredity and the capability of variation.

Heredity is conservative and tends to retain the ancestral characters. The capability of variation is influenced by external conditions and results in the modification of structures. The resulting adaptations as far as they are useful to the organism concerned, are transmitted to future generations. Thus heredity and adaptation are parallel factors, and the knowledge of this fact helps us to explain the presence of various rudimentary organs in the adult.

With these general principles in mind, the study of the comparative anatomy of the accessory cavities of the nose, should teach us what their function has been and whether or not they are now functionally active in man.

FISHES.—In fishes there are no accessory cavities of the nose. Their nose is a simple sack-like structure and does not communicate with the mouth, except in Dipnoi.

Dipnoi are fishes which live in shallow streams, and while in the water breathe through their gills as other fishes do.

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Their nose communicates with the mouth, and they have a functional lung and resemble reptiles in some other respects. In the dry season, they live in the mud and breathe through their nose, and thus the nose becomes a part of the respiratory system.

REPTILES.—In reptiles the nasal cavities are more complicated. Each nasal fossa is divided in a general way, into a respiratory portion, situated anteriorly, and an olfactory portion, situated in the posterior superior part of the nose. This olfactory region contains the sensory nerve cells, and a rolled turbinal springs from its outer wall.

BIRDS.—In birds the turbinals all show a higher degree of development. Their form varies greatly; some are simple prominences and some are decidedly scroll shaped or even present a double coil, the superior coil making one complete turn and the inferior coil making two or more turns within itself.

There are no accessory cavities of the nose, but the bones of the skull, like some of the other bones in birds, contain large air cells or cavities to make the bones lighter.

MAMMALS.—In mammals, the turbinals and the nasal accessory cavities exhibit great variations, each showing a high or low degree of development, according to the environment of the animal.

KANGAROO (Macropus.)—The kangaroo occupies quite a low position in the mammalian scale, but its nose is much more highly developed than the nose in any of the birds.

The nasal fossae are two symmetrical cavities completely separated from each other in the median line by the septum. The maxillary turbinals correspond to the inferior turbinals in man. There is one in the anterior part of each fossa. Each one projects outward and upward from the maxillary bone, beginning as a thin shelf-like process which divides into numerous curved branches partially filling the anterior half or respiratory portion of the nose (Plate I, Figures A and B, 2). The function of the maxillary turbinals is to prepare the inspired air for respiration.

The posterior part of the vomer gives off two lateral wings, one on each side, which extend across the nasal fossae and unite with the ethmoidal bones, thus dividing each fossa posteriorly into two superimposed cavities (Plate I, Figures C and D, 6). The superior cavities contain most of the ethmoidal turbinals and constitute the olfactory portion of the nose. The inferior cavities are tube-like structures and form a direct communication between the anterior or respiratory portion of the nose and the nasopharynx (Plate I, Figures C and D, 7).

There are five ethmoidal turbinals in each fossa. They spring from the convex surface of the cribriform plate of the ethmoidal bone and give off numerous branches which extend anteriorly into the nose. Some of them articulate with and are supported by the frontal, nasal and superior maxillary bones, but none of them unite with the septum (Plate I, Figures B, C and D, 3). The numerous branching and curved processes of the ethmoidal turbinals are all covered by olfactory mucous membrane and thus a large surface is exposed in a comparatively small area. The function of the ethmoidal turbinals is olfactory.

The maxillary sinuses are simple diverticula between the anterior inferior parts of the ethmoidal turbinals and the superior maxillary bones (Plate I, Figure C, 5). They can hardly be called sinuses, but are rather large channels which lead from the respiratory portion of the nose to the external portion of the ethmoidal turbinals and thus bring a large olfactory surface in direct communication with the inspired air.

The ethmoidal cells are spaces between some of the branches of the ethmoidal turbinals and the adjacent bones of the skull (Plate I, Figures B and C, 4). They communicate directly with the maxillary sinuses and thus conduct the air over a still greater surface of the olfactory turbinals.

There are no frontal or sphenoidal sinuses in the kangaroo's skull. Thus in the kangaroo, the olfactory or ethmoidal turbinals are situated in the posterior superior part of the nose. Their internal surfaces are exposed directly to a part of the inspired air after it has passed through the branches of the maxillary turbinal. The maxillary and ethmoidal sinuses; which are the only ones present in the kangaroo, serve as channels to conduct some of the inspired air over the external lateral surfaces of the ethmoidal turbinals and so expose these portions of the olfactory turbinals more directly to the inspired air and are, therefore, functionally active in increasing the acuteness of the sense of smell.

DEER (Cervus).

A longitudinal section through the deer's head shows three ethmoidal turbinals (Plate II, Figure A, 2), and a large maxillary turbinal (Plate II, Figure A, 1), all of which present comparatively smooth surfaces. Transverse sections through these turbinals show them to be highly developed and very complicated structures.

The maxillary turbinal is a double coil. It springs from the superior maxillary bone as a thin shelf-like process, parallel to the floor of the nose, extending two-thirds of the way across the fossa. It then divides into two processes, the superior one makes three complete turns within itself and the inferior one makes two turns (Plate II, Figures B, C, D and E, 1).

There are three ethmoidal turbinals (Plate II, Figures A, C, D, E, F and G, 2). They arise from the convex surface of the cribriform plate of the ethmoidal bone, and at first consist of a mass of thin, delicate curved branches which intertwine with each other and almost completely fill the posterior superior part of each fossa (Plate II, Figure G, 2). As these branches extend anteriorly, they decrease in number and present broader and less convoluted surfaces (Plate II, Figure F, 2). The ethmoidal cells are cavities contained within these broader branches or between these branches and some of the surrounding bones of the skull (Plate II, Figure F, 7). The frontal sinuses are comparatively small cavities between the plates of the frontal bones and are partially filled by scrolls of the ethmoidal turbinals.

The maxillary sinuses are large cavities in the superior maxillary bones (Plate II, Figure F, 6). Their ostia are situated in the posterior part of each cavity and open into the nose in conjunction with some of the ethmoidal cells. Some processes of the ethmoidal turbinals extend into the maxillary sinuses.

In the deer, the accessory sinuses are more circumscribed and more definitely separated from the rest of the nasal fossae than they are in the kangaroo, but the sinuses all contain ethmoidal turbinal tissue and are a part of the olfactory portion of the nose.

PRAIRIE WOLF (Canis latrans).

The wolf's nose is more highly developed than the nose of the kangaroo or the deer. The turbinals are all much more complicated and their branches are more numerous and convoluted so that the inspired air is brought in contact with a tremendous expanse of mucous membrane.

The anterior half of each nasal fossa is almost completely filled with the fine branches of the maxillary turbinal (Plate III, Figures A and B, 1). The lateral wings of the vomer divide the posterior portion of each nasal fossa into an olfactory and respiratory part as in the kangaroo and the deer (Plate III, Figures A, C and D, 17).

In each fossa there are seven ethmoidal turbinals radiating from the convex surface of the cribriform plate and their delicate intertwining scrolls form a dense labyrinth in the olfactory part of the nose (Plate III, Figures A, C and D, 2). They articulate with the lateral wings of the vomer, the superior maxillary, frontal and nasal bones.

The maxillary sinus (one in each fossa) is an irregularly oval cavity between the ethmoidal turbinals and the superior maxillary bone (Plate III, Figures C and D, 11). Its posterior part is entirely shut off from the nasal fossa by the ethmoidal bone but anteriorly it is only partially separated from the nose by some scrolls of the ethmoidal turbinal. It acts as a channel to conduct some of the inspired air over the external lateral surface of the olfactory turbinals and thus produces a keener sense of smell. It is therefore, a part of the olfactory portion of the nose.

The ethmoidal cells are irregular spaces between the ethmoidal turbinals and the surrounding bones of the skull and contain scroll-shaped branches of the ethmoidal turbinal which spring directly from the cribriform plate (Plate III, Figure A, 4),

There is one frontal sinus in each half of the skull. It is an irregular cavity between the two plates of the frontal bone (Plate III, Figure A, 6). Anteriorly it communicates directly with the ethmoidal cells and contains a double coil of the ethmoidal turbinal.

The sphenoidal sinus is simply a slight depression in the anterior part of the sphenoidal bone and is filled by an ethmoidal turbinal scroll.

All the accessory sinuses of the nose in the wolf are therefore a part of the olfactory portion of the nose and all contain olfactory turbinal tissue. Their function is to conduct the air over a part of the olfactory turbinals which would not be otherwise directly exposed to the inspired air, and thus increase the acuteness of the sense of smell.

APES. Indian Ape (Macacus rhesus).

The ape's nose is a very much degenerated structure. The maxillary turbinal is a slightly curved bone and is very similar in outline and position to the corresponding turbinal in man (Plate IV, Figure B, 1). There are two ethmoidal turbinals in each fossa (Plate IV, Figures A, B and C, 2 and 3). The larger one projects downward and forward from the ethmoidal bone and divides into two branches (Plate IV, Figures A, B and C, 2). The smaller one is more scroll-shaped but both of these turbinals have lost the numerous, fine, convoluted branches which are present in lower animals, and the other ethmoidal turbinals (third, fourth and fifth) have entirely disappeared.

The maxillary sinus is situated within the maxillary bone and opens into the middle meatus through a small ostium, considerably above the floor of the sinus. Its walls are smooth and it contains no ethmoidal turbinal tissue (Plate IV, Figures A, B and C, 10). The other accessory sinuses of the nose have disappeared completely and the space which they occupied in the frontal and sphenoidal bones in lower animals, is filled with cancellous bone.

GIBBON or long-armed Ape (Hylobates).

The gibbon's nose is less degenerated than the nose of many other apes. The maxillary turbinal has a double coil (Plate V, Figures A, B and C, 1). There are two well-defined ethmoidal turbinals (Plate V, Figures A, B and C, 2 and 3), and three small ethmoidal cells. The maxillary sinus is comparatively large and communicates with the nasal fossa through a small ostium, high up in the middle meatus (Plate V, Figures B and C, 10). The sphenoidal sinus is very large and opens into the superior meatus through a small ostium (Plate V, Figure A, 6). There are no ethmoidal turbinals in the maxillary or sphenoidal sinuses. The frontal sinuses are absent and in their place there is cancellous bone.

In apes, as a class, all the turbinals have degenerated and show a comparatively simple structure. The accessory sinuses present numerous variations. The maxillary sinus is always present and usually has smooth walls and a small ostium opening into the middle meatus. In some of the lower orders of monkeys, the ostium remains quite large and a small branch of the ethmoidal turbinal projects into the sinus.

The frontal sinus is present in the chimpanzee. In other apes it is absent and the frontal bone is cancellous.

The ethmoidal cells vary greatly in size and number. In some apes, there are none and the ethmoidal turbinals are very rudimentary. In others, there are several ethmoidal cells and the ethmoidal turbinals are not so much degenerated as they are in the apes, which have no ethmoidal cells. The variations in the sphenoidal sinuses are similar to those in the ethmoidal cells. In those apes in which these sinuses are absent, the ethmoidal turbinals are more degenerated and the ethmoidal cells are also absent.

MAN.

The general characteristics of the accessory cavities of the nose in man are well known. They present numerous variations, many of which are reversions to more primitive types. The absence of one or both frontal sinuses corresponds to the absence of these sinuses in most apes. The ethmoidal sinuses are cells surrounded by some of the numerous branches of the ethmoidal and adjacent bones and occasionally contain small ethmoidal turbinal scrolls, as they always do in such animals as the wolf. The subdivision of one or both sphenoidal sinuses into two or more cavities corresponds to a similar division of these sinuses in some of the lower animals in which the ethmoidal turbinals extend into the sphenoidal sinuses and produce numerous subdivisions. The irregular ridges sometimes seen on the lateral walls of the maxillary sinuses are probably rudiments of the ethmoidal turbinals which extend directly into the sinuses in some animals, and in certain species are attached to the sinus walls.

The accessory sinuses in the lower animals are developed, therefore, in conection with the olfactory portion of the nose. They are rather simple channels which conduct some of the inspired air over the external lateral surfaces of the olfactory turbinals.

In animals which have an acute sense of smell, the olfactory (ethmoidal) turbinals exhibit a tremendously intricate development and the accessory sinuses are correspondingly more highly developed, and all of them contain olfactory turbinal tissue. Their function is to conduct the inspired air more directly over a large surface of the olfactory turbinals, which would not otherwise be exposed to the air except by diffusion, and thus the accessory sinues increase the acuteness of the sense of smell.

In those animals in which the sense of smell is not acute, the olfactory turbinals have degenerated and receded from the accessory cavities. The cavities are left with comparatively smooth walls, their openings into the nasal fossae contract and their functional activity is lost.

In man the accessory cavities are almost completely shut off from the nose, their functional activity ceases, and they remain as rudimentary structures.

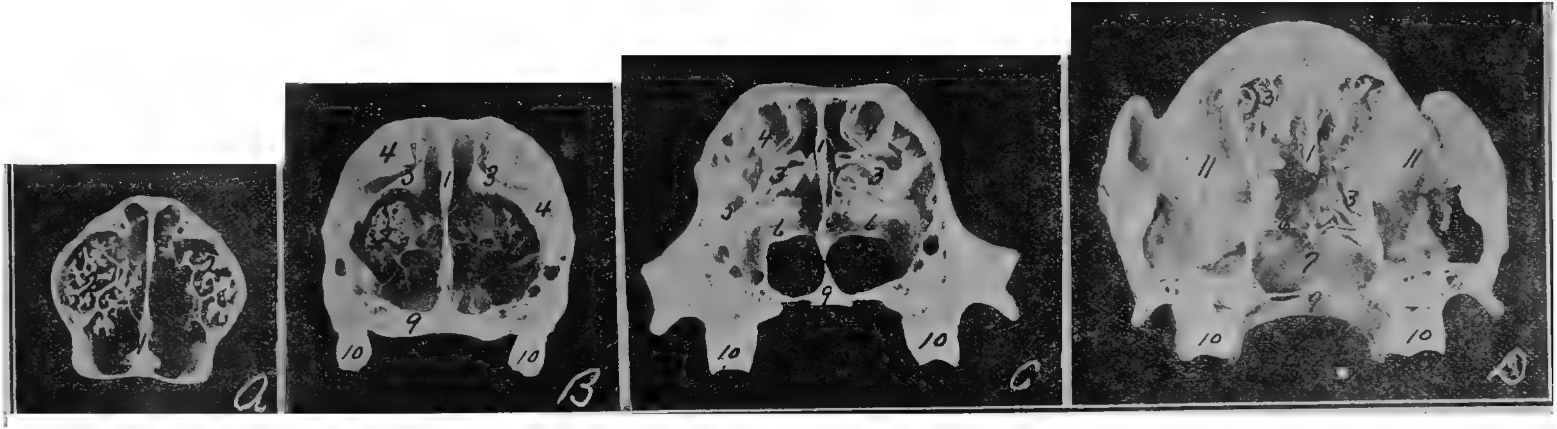

PLATE I KANGAROO (Macropus).

Transverse sections through a kangaroo's skull, showing both nasal fossae. A and B, looking anteriorly; C and D, looking posteriorly.

1. Nasal septum.
2. Maxillary turbinals.
4. Ethmoidal sinuses.
5. Maxillary sinuses.
6. Lateral wings of vomer.
7. Respiratory tract in the posterior inferior part of the nose.
8. Cribriform plate of the ethmoidal bone.
9. Palate.
10. Teeth.
11. Orbit.

PLATE II DEER (Cervus).

A. the left nasal fossa of a deer. B to G, transverse sections through both nasal fossae of a deer. B, D, E, F and G, looking posteriorly. C, looking anteriorly.

1. Maxillary turbinals.
2. Ethmoidal turbinals.
3. Brain cavity.
4. Posterior nares.
5. Septum.
6. Maxillary sinus.
7. Ethmoidal cells.
8. Palate.
9. Teeth.
10. Orbit.
11. Lateral wings of vomer.

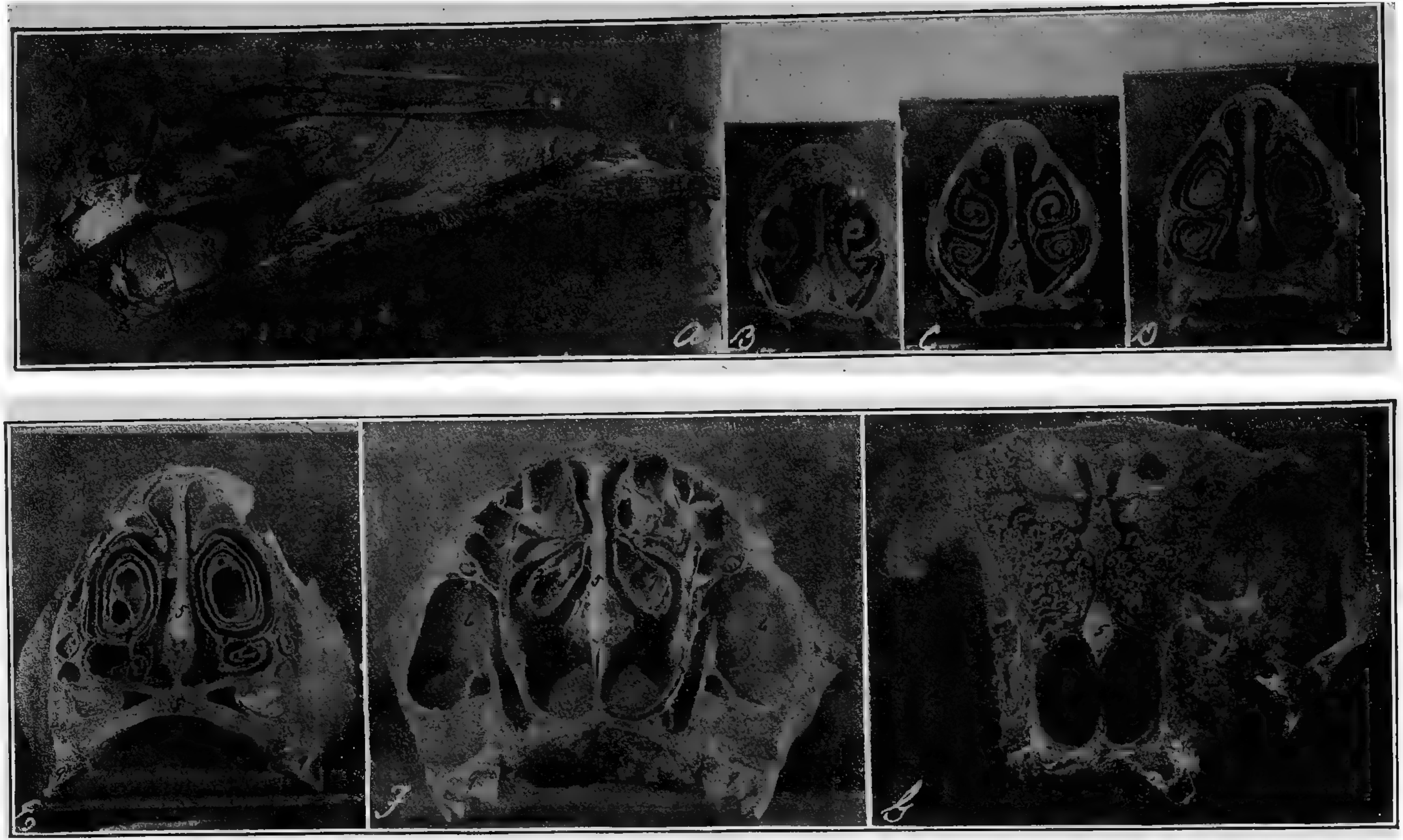

PLATE II

PLATE III. PRAIRIE WOLF (Canis latrans).

A, longitudinal section through a wolf's skull, showing the right nasal fossa. B, C and D, transverse sections through a wolf's skull showing both nasal fossae. B and C, looking anteriorly; D, looking posteriorly. (In Fig. B, the nasal septum is absent, having been lost in maceration.)

1. Maxillary turbinal.
2. Ethmoidal turbinal.
3. Ostium maxillare.
4. Ethmoidal turbinal in ethmoidal cells.
5. Ethmoidal turbinal in frontal sinus.
6. Frontal sinus exposed by removing its internal wall.
7. Cribriform plate.
8. Ethmoidal turbinal in sphenoidal sinus.
9. Brain cavity.
10. Posterior nares.
11. Maxillary sinus.
12. Ethmoidal turbinal extending into the maxillary sinus.
13. Orbit.
14. Palate.
15. Teeth.
16. Vomer.
17. Lateral wings of vomer.
18. Septum.
19. Respiratory tract in the posterior inferior part of the nares.

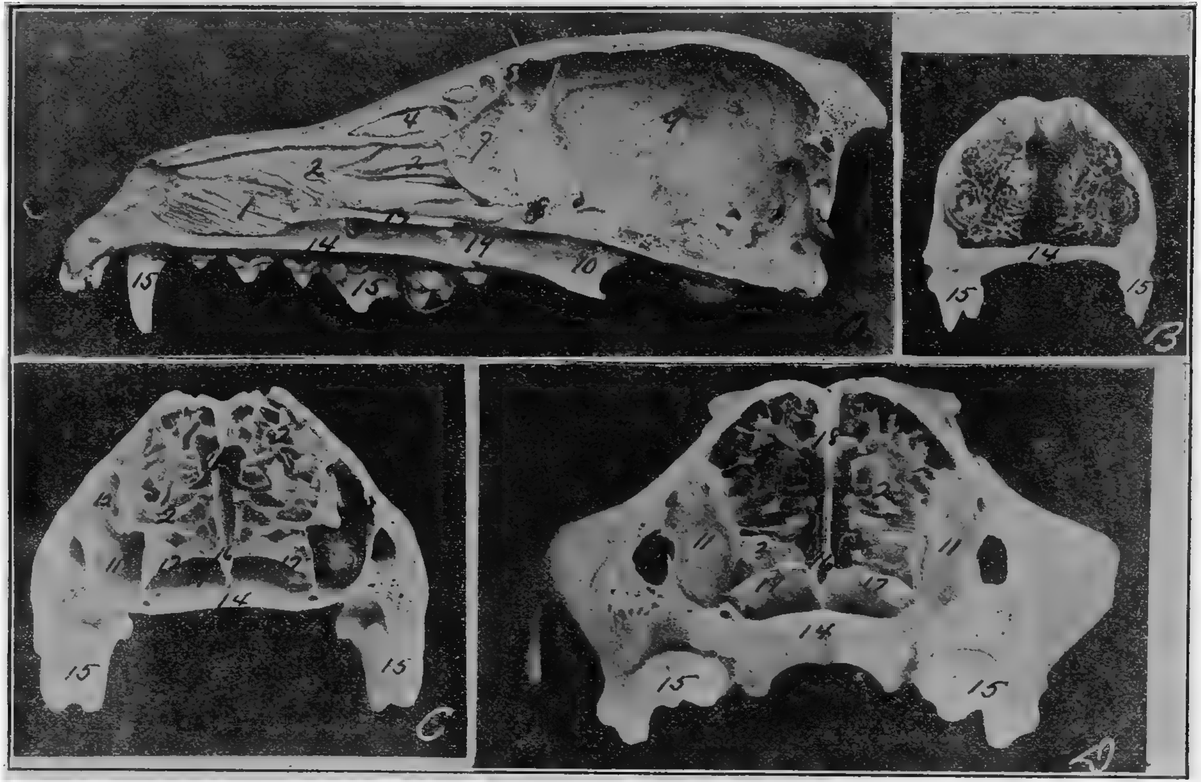
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PLATE III.

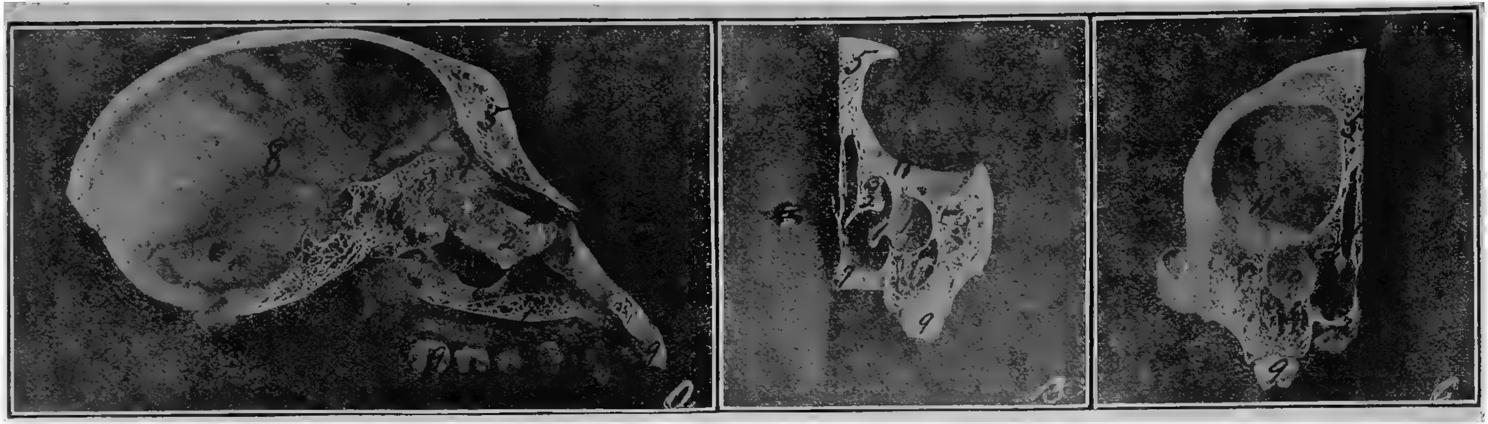

PLATE IV. INDIAN APE (Macacus rhesus).

A, longitudinal section through ape's skull, showing the left nasal fossa. B and C, transverse section through the right nasal fossa of an ape. B, looking anteriorly; C, looking posteriorly.

1. Maxillary (inferior) turbinal.
2. Ethmoidal (middle) turbinal.
3. Ethmoidal (superior) turbinal.
4. Cribiform plate of ethmoidal bone.
5. Cancellous frontal bone.
6. Cancellous sphenoidal bone.
7. Palate.
8. Brain cavity.
9. Teeth.
10. Maxillary sinus.
11. Orbit.
12. Nasal septum.

In Fig. A, the maxillary turbinal has been lost in maceration and the maxillary sinus (10) is exposed.

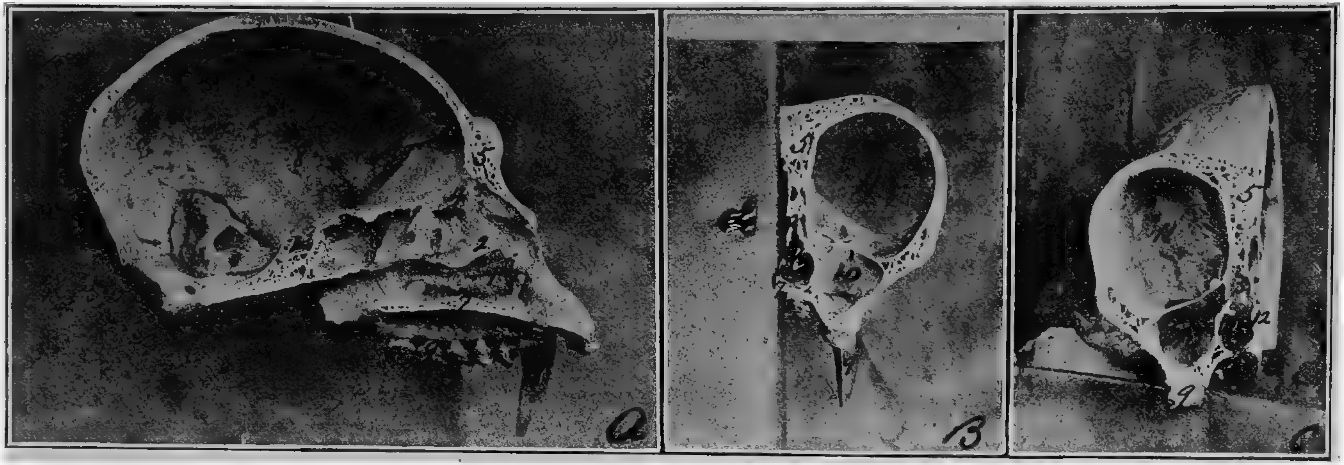

PLATE V. GIBBON (Hylobates.)

A, longitudinal section through a gibbon's skull, showing the left nasal fossa. B and C, transverse sections through the right nasal fossa of a gibbon. B, looking anteriorly; C, looking posteriorly.

1. Maxillary (inferior) turbinal.
2. Ethmoidal (middle) turbinal.
3. Ethmoidal (superior) turbinal.
4. Cribriform plate of ethmoidal bone.
5. Cancellous frontal bone.
6. Large sphenoidal sinus.
7. Palate.
8. Brain cavity.
9. Teeth.
10. Maxillary sinus.
11. Orbit.
12. Nasal septum.

TWO CASES OF BONE IMPACTED IN THE LARYNX.*

BY J. M. INGERSOLL, A.M., M.D., AND DUDLEY P. ALLEN, A.M., M.D.,
CLEVELAND, OHIO.

Foreign bodies in the larynx usually cause such distressing symptoms that relief is hastily sought and, in most cases, promptly secured by the removal of the foreign body.

Quite a number of cases however, have been reported in which a foreign body has remained in the larynx for a period of time varying from a few months to several years. One of the characteristic features of such cases is the fact that the larynx soon shows a remarkable tolerance for the foreign body. If there has been no interference with phonation or respiration, the primary laryngeal irritation may be entirely forgotten by the patient and the persistence and severity of the symptoms caused by the secondary pathological conditions in the larynx or in the bronchi and lungs, mask completely the primary cause of all the trouble.

Case I. In a case recently seen by us, we must frankly confess that the possibility of a foreign body in the larynx was not considered at any time until it was found at the autopsy. The patient was a well-developed man, thirty-seven years old. He was brought to Lakeside Hospital one night on account of marked inspiratory dyspnoea. The difficulty in breathing had begun eight days before and had steadily increased. A few hours after his admission to the hospital, he became cyanotic and it was necessary to do a tracheotomy at once. The following day, an examination of the larynx revealed a complete bilateral abductor paralysis. As the cords were in apposition, no view of the inferior part of the larynx or the trachea was obtained. The larynx, above the cords, was inflamed and two ulcerations were seen. Moist rales could be heard throughout the chest and there was some increased dulness at the right apex. Otherwise, the man was in good condition. He had had syphilis several years before.

It was thought that the laryngeal paralysis was due to pressure from a gumma, for in the absence of any demonstrable cause this seemed to be quite probable especially as the man had a syphilitic history, and so he was given iodide of potassium This had no effect upon the laryngeal paralysis. The condition in the lungs grew steadily worse and the patient died of septic pneumonia about one month after his admission to the hospital.

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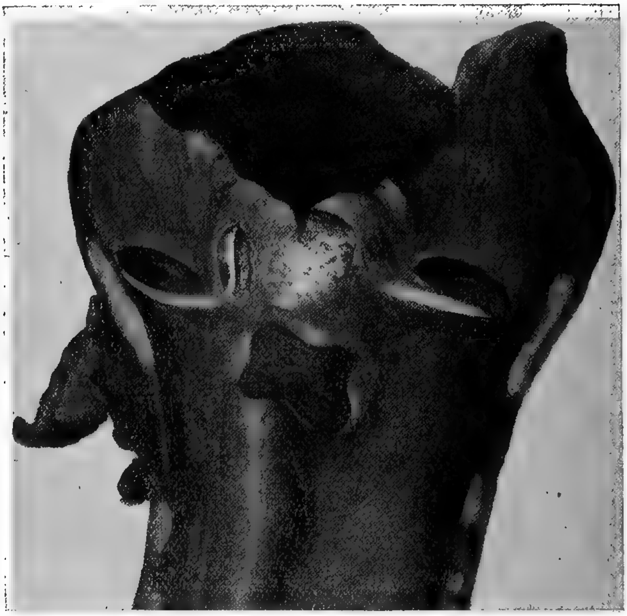
* Read before the 28th Annual Congress of the American Laryngological Association, Niagara Falls, New York, May 31, June 1 and 2, 1906.

The autopsy was made by Dr. David Marine, resident pathologist, to whom I am indebted for the following abstract of the post-mortem findings.

ANATOMICAL DIAGNOSIS.

1. Foreign body (bone) in the larynx, lodged in an ulcerated cavity situated posteriorly and transversely between the cricoid cartilage and the oesophagus.



A Piece of Bone Impacted in the Tissue Around the Larynx.

Case. I. The larynx has been opened anteriorly a little to the left of the median line. The piece of bone is shown projecting out beyond the right side of the larynx. On the posterior wall of the larynx, there is a deep ulcerated cavity through which the piece of bone can be seen. Just above this cavity, a superficial ulceration, covering almost all of the inter-arytenoid space, is shown. Another superficial ulceration can be seen above the posterior end of the right vocal cord.

2. Consolidation with necrosis and liquefaction (gangrenous abscess) of the lower and middle lobes and lobular consolidation of the upper lobe of the right lung.
3. Chronic quiescent tuberculosis of the left apex.
4. Acute hemorrhagic bronchitis and trachitis.
5. Gumma of the right lobe of the liver.
6. Moderate acute splenic tumor.

7. Cloudy swelling of the liver and kidneys.
8. Chronic atrophic gastritis.
9. Tracheotomy wound.
10. Early arteriosclerosis.
11. Chronic thyroiditis.

In the posterior wall of the larynx, a little below the vocal cords, there was an ulcer, about two centimeters in diameter, opening into a cavity containing a piece of cancellous bone which extended two-thirds of the way around the larynx. The edges of the ulcer were cicatrized showing that it must have existed for some time.

The piece of bone was irregularly triangular in shape, about five centimeters long and two centimeters wide in its greatest measurements, and its average thickness was about one-half of a centimeter. It was curved on its flat surface and the concavity was turned toward the larynx.

The oesophagus was intact and its mucous membrane was normal. If the piece of bone had passed from the oesophagus into the tissue around the larynx, the oesophagus would have contained some cicatrix.

It seems probable therefore, that the piece of bone had fallen into the larynx while the patient was eating and then had worked its way through the posterior wall of the larynx into the position in which it was found at the autopsy.

The man gave no history of such an accident having occurred, but this is apparently the only possible explanation of the presence of the piece of bone in the larynx. The accident had probably occurred several months or a year before the laryngeal paralysis developed and it had been forgotten by the patient so that he did not attribute the difficulty in breathing to any previous laryngeal condition.

The bilateral abductors paralysis was caused by inflammatory induration and pressure of the bone on both recurrent laryngeal nerves. The pneumonia and gangrene of the lungs were due to the septic infection from the larynx.

The cicatrized edges of the ulcer and the position of the bone, buried deep in the tissue around the larynx, both bear evidence to the fact that the bone must have been in the larynx a long time.

Case II. The following case was seen by Dr. Dudley P. Allen, ten years ago, but has not been reported before.

The patient was a married man, thirty-one years old. He had always been healthy and had had no serious trouble with his throat. On the 12th of February, 1896, he noticed some difficulty in speaking and by the 16th of February, he was unable to speak above a whisper. He began to notice some inspiratory dyspnoea which continued until the time of operation in July. At times, the dyspnoea was quite marked.

On April 13th, he went to Hot Springs, Arkansas. A diagnosis of syphilis was made and he was given large doses of iodide of potassium and also had inunctions of mercury daily for forty days. He returned home on May 26th, and a laryngologist who saw him then thought that the condition in the larynx was malignant.

He entered Charity Hospital on May 31st, and a tracheotomy was performed to relieve the dyspnoea. He was given anti-syphilitic treatment again but a careful study of the case led to the conclusion that it could not be specific, and there did not appear to be any positive evidence of its being a malignant growth of the larynx. The appearance of the larynx was difficult to explain. A grayish roughened surface could be seen below the vocal cords, and the latter were injected and thickened.

The question of extirpation of the larynx was considered, but before doing this, it was thought wise to split the larynx in order to ascertain more definitely the exact nature of the disease. On July 2nd, the larynx was divided in the median line and an irregularly shaped piece of bone was found imbedded in the right side of the trachea just below the larynx.

The bone was a little over two centimeters long and about one centimeter wide. In splitting the larynx, the anterior attachment of the right vocal cord was somewhat injured, so that it was stitched into place with a catgut suture. The trachea was then united and the incision closed. The tracheotomy tube was left in place for about two weeks after the operation. It was then removed and the patient was discharged.

He did not know when the piece of bone had fallen into his larynx; he did not remember having had any attack of choking or severe coughing nor had he been intoxicated and thus offered a chance for the bone to become imbedded in the trachea without his being conscious of it. His relief after the operation was immediate and complete.

The patient was re-examined on May 3rd, 1906. He has been perfectly well since the operation. The larynx seems to be about normal. Both vocal cords move freely and meet each other in the median line. He says that he cannot speak as loud as he could before the operation and his voice tires a little more easily.

318 Euclid Ave.

A NEW SIGN FOR THE DETECTION OF MALINGERING AND FUNCTIONAL PARESIS OF THE LOWER EXTREMITIES.

C. F. HOOVER, M.D.
CLEVELAND.

The sign I wish to describe is one which I have employed for the past two years. Although the cases observed number only four, I feel justified in attaching great importance to the sign because it is dependent on a normal function, which I find always exhibited in healthy persons and invariably present in the sound leg of patients suffering from hemiplegia or paresis of one leg due to some pathologic lesion.

If a normal person, lying on a couch in the dorsal position, be asked to lift the right foot off the couch with the leg extended, the left heel will be observed to dig into the couch as the right leg and thigh are elevated. If you place your hand under the tendo Achillis of the left side and sense the muscular resistance offered by the left leg you will observe that the left heel is pressed on to the couch with the same force which is exhibited in lifting the right leg off the couch. In other words, the left heel is employed to fix a point of opposition against the couch during the effort at lifting the right leg. This will always occur if the healthy person makes a free and uninhibited effort to lift the right leg. Of course the opposition offered by the other leg is not essential to a successful elevation of one leg, but if a free effort of the will is made (no matter how slight the effort) the point of opposition made with the leg of the other side is invariably present unless some inhibitory impulse be sent to the opposing leg.

If the movements are carried out in the reverse order the same principle holds true; i. e., if a normal person be requested to press the right leg against the surface of the couch there will be a counter-lifting force exhibited in the left leg.

If a patient suffering from hemiplegia or monoplegia of a leg be requested to lift the extended and paretic leg off the couch it will be observed that the other leg offers the opposition above described whether there is any voluntary muscular strength exhibited or not on the affected side. I have had opportunity to observe this in a large number of hemiplegic patients and the opposition from the normal leg never failed.

If the hemiparetic patient is asked to lift the normal leg off the couch against resistance he will exhibit an opposition with the paretic leg which is directly proportional to the voluntary muscular strength he is able to employ when a display of voluntary muscular power in the paretic leg is exacted.

When the upper extremity is involved this sign is sometimes demonstrable on the normal arm, but at other times it is wanting.

In two cases in which paresis of one leg was claimed by the plaintiffs in suits for personal injuries, there were wanting the characteristic physical signs to sustain the claim of paresis of the lower extremity as the result of injuries. Furthermore, in both of these cases, when the patient was asked to lift the normal leg off the couch, the leg which was alleged to be very paretic was opposed strongly against the surface when resistance was offered to lifting the normal leg. When the patient was requested to lift the paretic leg, there was an apparent attempt to respond to my demand, but the normal leg did not offer the least opposition. The normal leg lay perfectly limp on the couch. Had the paresis been genuine, the sound leg would have been firmly opposed against the surface of the couch when an uninhibited attempt was made to lift the paretic leg.

The absolute lack of complemental opposition from the normal leg was also observed in a case of hysterical hemiplegia, when the patient was requested to lift the paralyzed leg.

In another case of hysterical para-paresis inferior, which was accompanied by abasia, the patient could bow himself into the pose of opisthotonos, but if he was requested to lift one leg off the couch there was no complemental opposition offered by the other leg and the leg which he seemingly attempted to lift would not be raised off the couch.

This sign appeals to me as being particularly valuable for the reason that it depends on the exhibition of a function from the normal leg which must always be present if the patient does not inhibit the normal impulses to the lower extremities.

In the four cases I have briefly described the complemental opposition was entirely wanting. Whether this lack of complemental opposition will always be found or not in malingerers and hysterical subjects remains for further observation to determine. But in view of the fact that complemental opposition is always present in a normal patient and in all patients with genuine paresis and genuine paralysis, we are justified in assuming the existence of cerebral inhibition to an apparent voluntary exhibition of strength when complemental opposition is absent.

If a malingerer were familiar with the object of the examination he could, of course, satisfy the demands of the examiner. In testing for this sign the examiner should seem to fix his attention on the leg which is alleged to be paretic.

In this manner I believe that one will always be able to trick a malingerer or hysterical subject into betraying the falsity of his claim.

I demonstrated the character and significance of this sign to one of the patients described. He promptly abandoned a crutch and cane, an orthopedic corset and blue spectacles and returned to work for the company against whom he had brought suit. The same course was adopted with the hysterical abasic patient. His gait became quite normal after a half hour's persuasion. Whether he later relapsed or not I do not know.

The sign in genuine hemiplegia which Babinski describes[1] for differentiating between genuine and functional hemiplegias depends on the affected side for its exhibition. I have found Babinski's sign unsatisfactory. The fact that this sign of complemental opposition is always present in normal subjects and in genuine paresis of the lower extremity, and the fact that it depends on an invariable function of the normal side gives it a very broad application.

702 Rose Building.

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[1] Brissaud and Souquis: Article in Bouchard and Brissaud's "Traité de médicine," ix, 55.

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ARTERIAL CHANGES IN CHRONIC INTERSTITIAL NEPHRITIS.

BY C. F. HOOVER, M. D.,
Cleveland.

[Read before the Ohio State Medical Association, Columbus, 1908.]

The vascular phases of chronic interstitial nephritis comprise all the particular aspects which a failing hydraulics of blood circulation may present. The ultimate results, so far as nutrition and function of the heart and kidneys are concerned, are discussed under other titles.

Several of the early phases and some of the nervous phases of the disease will occupy the time assigned to me for discussion of the subject before you. If we conceive chronic interstitial nephritis to be a mere incident in the natural history of a chronic cardio-vascular sclerosis, I believe we entertain a view which is consistent with most of the clinical histories of the disease. A very common story told by patients who acquired the disease between forty and fifty years of age reveals an account of sick headache or migraine from early youth. The frequency of the attacks diminishes gradually from late adolescence until the middle of the third decade; then the headaches cease and the patient begins to suffer from gaseous dyspepsia, which includes symptoms from both the stomach and intestine. In middle life the patient is no longer distressed by migraine, and the gastro-intestinal dyspepsia is less distressing, but now there develop the first signs of vascular erethysm. The patient finds he has neither the physical nor mental endurance which he formerly enjoyed. He finds his muscles are sore and stiff in the early morning. He awakens less refreshed from a night's sound sleep, and as the day wears on he suffers more from mental and physical exhaustion than is consistent with his age and state of general nutrition. The accessible arteries at this period do not reveal the hard and wiry character seen in advanced cases. The pulse may reveal only a slight prolongation of the katacrotus, and this prolongation is perceived only during the latter portion of the descending wave. The first impression such a pulse gives to the examiner's finger is like the bounding pulse of aortic sclerosis. It is a pulsus celer, but the celerity is estricted to the anacrotus and the first portion f the katacrotus. During this phase of the disase there is generally a capillary pulse plainly perceptible. This partial celerity of the pulse wave and the capillary pulse together may be crease in the peripheral resistance unless one carefully observes the excursion of the brachial artery at the bend of the elbow, where we can always see an exhibition of pulse characteristics more faithfully portrayed than in a sphygmogram. The brachial artery is visible because of the accentuated curves in its course. We can here see the rapid anacrotus and the rapid katacrotus during two-thirds of the distance and then a final tardy descent to the abscissa.

This is not an invariable experience, but certainly a very common event in the clinical study of chronic interstitial nephritis. The maximum blood pressure is high, but the heart at this period reveals only a slight increase in its dimensions. The patient says he can go through a set form of athletic exercises without suffering dyspnoea, but he complains of a feeling of tire at night-time which is quite out of keeping with his physical resources.

An examination of the urine at this period will often reveal no albumin nor casts. The urine secreted when the patient is lying down may contain no albumin, but urine secreted while the patient is going about will contain a trace of albumin and hyaline casts.

This period of vascular erethysm is the stage in which recognition of the disease is most important, because the disease may be arrested by a suitable regimen in diet and the employment of nitrites and hot baths for lowering peripheral arterial resistance. This period of the disease often escapes detection because there are several features of the physical signs which seem inconsistent with an increase of the arterial resistance. The pulse in the radial artery is always insufficient for estimating or detecting a heightened arterial pressure. The terminal delay in the descent of the pulse wave is underestimated unless the examiner will make a careful inspection of the brachial artery where the complete excursion is visible. For an estimation of the pressure, the femoral artery at Poupart's ligament and Scarpa's triangle is most suitable. We have here a large artery (superficially located), which can be opposed to the bony surface underneath. I have found (by employing a sphygmomanometer as control) that the blood pressure can be estimated very accurately at this point. An estimate made from palpation of the femoral artery will not vary more than 20 mm. from the results obtained with the blood pressure apparatus. From the radial artery one cannot form an approximate estimation of the maximum blood pressure. One may make a very nice analysis

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There are two points about the precordial area which are also very misleading in the erethistic stage of the disease. Although the maximum blood pressure may be as high as double the normal, the aortic second sound is not accentuated, nor is the closure of the aortic valves palpable over the second intercostal space at the right of the sternum. Later in the disease, when the aortic arch will have become dilated and elongated, the aortic second will be distinctly palpable and audible, without any further increase in the blood pressure. This is due purely to the increased accessibility of the aortic wall and not to any heightening of the blood pressure.

The size of the heart is also misleading, but if careful and exact percussion is employed we can determine an extension of the precordial dullness fully an inch to the left. We must remember at this period of cardio-vascular disease we are dealing with a concentric hypertrophy and the heart itself may weigh quite as much as at a later period when the increase in the precordial area is easily perceived by palpation.

The difference in the physical signs over the heart in the two periods are due to a concentric hypertrophy in the early period and an excentric hypertrophy in the later period.

The key to the whole situation lies in inspecting the brachial artery and palpating the femoral artery. During recent years many writers have declared the sphygmomanometer the only means by which one can form a correct judgment of the maximum blood pressure and just such cases as I have described are offered as evidence. The aortic second was not palpable nor audible, the precordial area showed only a slight or doubtful enlargement to percussion, the character of the radial pulse did not betray any signs of an increased peripheral resistance, but in spite of all this negative evidence, the blood pressure apparatus revealed a maximum pressure fully double the normal. The error lies with the examiner and not with the cardio-vascular system. If one will look to the brachial artery for his pulse characteristics and palpate the femoral artery for an estimation of blood pressure he will escape the error. Although these details seem insignificant, they are very important, for the recognition of chronic interstitial nephritis during the period of vascular erethism, when the urine shows no signs of disease, is a matter of vital importance to the patient. Later in the course of the disease the symptom-complex associated with chronic interstitial nephritis is that of vascular crisis. Vascular crises play the most conspicuous role in the history of some cases of chronic interstitial nephritis. I have had one man under observation for the past nine years who has had one attack of transient amaurosis, one attack of aphasia which lasted only several hours, two attacks of complete hemiplegia from which he recovered in a day and several transient pareses of one arm or the other. It is these vascular crises which have been so misleading and have introduced so many confusing complications into our conception of uraemia.

Ascoli of Genoa published a monograph of 275 pages on the subject of uraemia. In this monograph Ascoli attempts to introduce some orderly classification of varying pictures of uraemia. When the reader has finished with Ascoli's work I am sure he must share with me the opinion that Ascoli has failed to dispel the mist. In fact Ascoli shows that many symptoms of uraemia arise independently of the renal function so far as we are able to learn from the quantity of urine and urinary constituents. The whole classification of uraemias as pictured by Ascoli would be greatly simplified if all the symptoms due to vascular changes in the central nervous system (and falsely ascribed to uraemia) were taken out of the uraemia budget.

All the signs of uraemia are manifested through some effect on the central nervous system. The nervous symptoms of uraemia are so striking that the mass effect of these symptoms have compelled us to assign uraemia as a cause for all nervous symptoms in the clinical course of nephritis. I feel sure nothing could be further from the truth.

The two structures of the body which are most sensitive to an impairment of oxygen supply are the myocardium and gray matter of the central nervous system. One of the most striking instances to prove this statement is seen in carbon monoxide poisoning. Severe encepholo myelitis results from CO poisoning. The deleterious results to the central nervous system cannot be due to a want of nutrient plasma, for this is unmodified by the poisoning. But the oxygen content of the red cells is not given up to the tissues in CO poisoning, and, although the intravascular and extra vascular circulation may be perfectly normal, only one object of the circulation is defeated, viz., the oxygen supply to the with severe symptoms from an encephalomyelitis.

The only structures which suffer permanent injury from a temporary arrest of heart beat of two minutes, are those of the gray matter of the central nervous system. If we understand the central nervous system to be so sensitive to an impairment in its oxygen supply, it does not require a wide flight of the imagination to see how the function of any given portion of the cerebral cortex would suffer if its vascular supply should exhibit the same symptoms we are accustomed to see in Raynaud's disease, and erythromelalgia and akroparesthesia, and regional spasm of the entire vascular supply of one extremity from disease of the brain as I have seen in one case of brain syphillis.

The only visible arteries in the body are the retinal arteries and fortunately these arteries have been observed in a contracted state during transient amaurosis. **Pal** describes one case of his own (*in* his monograph on vascular crises) and also refers to two cases reported by other men. During the last year I saw a young woman 25 years old who had suffered three attacks of amaurosis which came on in the early morning and lasted for 24 hours. A very capable opthalmologist saw the eye ground during the first attack and told me that the retinal arteries and veins were so diminished in size that they seemed like small threads. With the return of sight this patient suffered from such a high degree of photophobia it was impossible to examine the eyes with an opthalmoscope. She gave evidences of many functional disturbances of the central nervous system besides those ascribable to vascular crises, but she serves the purpose of proving the presence of a contraction crises in the arteries of a sharply defined region. The case of Murphy of Chicago proved the same phenomenon in the splanchnic arterial distribution. This patient was operated upon for intestinal obstruction; at the operation a section 18 inches long of the ileum was found firmly contracted and pale. Warm cloths were applied to the affected part and as the vessels dilated the wall of the intestine relaxed. Lead colic was suspected and confirmed by further examination. We are perfectly familiar with vascular crises in the extremities, in the splanchnic arteries and in the retina, although the physiologists are not united in ascribing an active vaso-motor supply to the cerebral arteries, we know the anatomical basis exists for it, we can offer abundant clinical evidence for it and some physiologists have succeeded in demonstrating it experimentally.

chronic interstitial nephritis may have general vascular crises which are quite independent of a disturbed kidney function, but in former years these vascular crises were regarded as transient evidences of impending uraemia.

The patient (whom I first described in the paper as having had a series of regional vascular crises of the brain) was shopping in a down town store three years ago, when he suddenly became confused. He was unable to talk connectedly, his face was flushed, he was compelled to sit in a chair, he was very apprehensive and emotional. The patient was taken to the hospital where we found the arterial pressure was 250 mm. Hg., but I believe it was much higher an hour previous to the time the blood pressure was measured. The urine secreted during this period of high arterial tension had the same sp. gr. as that secreted twenty-four hours later when the arterial pressure was reduced to 150 mm. Hg. under the influence of trinitrin, hot baths, saline cathartics and a milk diet. This patient has been leading the life of a valetudinarian for the past eight years on account of cardio-vascular disease associated with slight albuminuria and a few hyaline casts. He will ultimately die with a chronic interstitial nephritis, but the nephritis will have been a small factor in his invalidism and cause of death. This patient serves the purpose of showing the dissociation between vascular and renal symptoms in the clinical cause of a disease in which we have been accustomed to ascribe all symptoms to a defective renal function.

As the sclerosis becomes more severe the patient may suffer from functional ischaemia of the brain and myocardium and ultimately a nutritive ischaemia of the brain or myocardium will terminate the scene.

Among the nervous symptoms often ascribed to uraemia are Cheyne-Stokes or Biot's respiration. I recently saw a patient 65 years old suffering from cardio-vascular sclerosis and nephritis whose chief complaint was dyspnoea. His dyspnoea or rather hyperopnoea alternated with apnoea. Apnoea lasted for fifty seconds and then followed the distressing hyperopnoea with air hunger which came and went with the characteristic crescendo and decescendo rhythm of Cheyne-Stokes respiration. This man had chronic interstitial nephritis, but the Cheyne-Stokes respiration during his waking and sleeping hours was not in any way dependent on an impaired kidney function. This patient had marked sclerosis of his bulbar arterial supply and the Cheyne-Stokes respiration was merely a symptom of the hypoesthesia of his respiratory center respiratory center. The patient was relieved of his Cheyne-Stokes symptom by large doses of trinitrin and caffeine citrate without modifying his oedema or diuresis.

The patient died from myocardial exhaustion a few weeks later, but had no return of the apnoea.

Another instance which illustrates the same point occurred in a man seventy years old who for two weeks had exhibited Cheyne-Stokes respiration with long periods of apnoea, and complete mental aberration. His physician remarked, "The man has such severe uremic symptoms and yet he secretes an abundance of urine with a normal sp. gr." Large doses of nitrites and caffeine citrate caused a disappearance of the mental and respiratory symptoms. The man died suddenly a few days later from myocardial exhaustion.

In former years I would have regarded both these patients as examples of uremia. I now feel certain these symptoms are secondary to an impaired arterial supply to the brain and sustain no relation to nephritis.

If we will always take the pains to differentiate between symptoms dependent on a diseased arterial system and those secondary to the insufficient renal function we will find the symptoms of uremia are not very complicated. The complication lies in a confusion of symptoms (caused by the kidney) with symptoms caused by the arterial disease.

PAROXYSMAL HEMOGLOBINURIA.

ACCOUNT OF TWO CASES.

C. F. HOOVER, M.D., AND C. W. STONE, M.D.
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The first of the two patients, A, who furnish the basis of this report is a man 29 years old, who was born in Hungary, and served as a soldier in that country. During his military service he suffered much from chilblains during the winter, but he never had an attack of hemoglobinuria until December, 1902, eight months after coming to America.

During the summer of 1902 he lived in Saginaw, Mich., where he suffered much from mosquito bites.

There is absolutely no history of any infection or illness until December, 1902, when the patient first observed the attacks of hemoglobinuria, which were invariably associated with exposure to cold. We had no opportunity to observe any chilblains in this patient, but he says that when his feet or hands are thoroughly chilled they become very white, then blue and finally red, swollen and feverish. The swelling lasts several hours. According to the patient's account of himself, such an attack is always followed by a "black-water" attack.

Besides the chilblains there is nothing unusual in the history of paroxysmal hemoglobinuria of this patient. We found that attacks could be produced by exposure to cold. If the patient placed both hands in ice cold water for five minutes no hemoglobinuria followed. Sitting before an open window for fifteen minutes, clad in hospital garb, when the out-door temperature was about 10 degrees C., was followed by a characteristic chill, fever and hemoglobinuria. If one foot was placed in a pail of water, 8 degrees C., for thirty minutes an attack would follow. During the interim the patient's blood showed a coagulation time of three and one-half minutes. Directly after an attack, while the temperature was still elevated, the coagulation time was the same.

On March 3, 1908, the patient's blood-count was the following:

W. B. C., 7,800.	R. B. C., 4,520,000.
Hb. (Sahli), 92.	Tallquist, 85.

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*Read in the Section on Practice of Medicine of the American Medical Association at the Fifty-ninth Annual Session, held at Chicago, June, 1908.

A differential count of 200 white cells gave the following results:

Polymorphonuclear cells,	158 =	79 per cent.
Small lymphocytes,	31 =	15.5 per cent.
Large lymphocytes,	8 =	4 per cent.
Eosinophiles,	3 =	1.5 per cent.

Repeated search for blood parasites proved negative, as did also all attempts to cultivate any organisms from the blood by the usual methods employed for such purposes. These examinations were made during the attacks and during the interims. On March 13 an attack was produced by placing the patient's foot in a pail of water at 8 degrees C. The following observations were made before, during and after the induced attack of hemoglobinuria.

The patient's foot was placed in the water at 10:50 a. m. Although there were some subjective premonitory signs of a chill at 11:50 it was not until 11:55 that the rigor was pronounced.

The temperature by mouth was:

At 10:20 a. m., 98.3 degrees.
At 11:20 a. m., 97.6 degrees. Subjective symptoms of muscular soreness.
At 11:50 a. m., 97.4 degrees. Chill apparent.
At 12:24 p. m., 100.2 degrees. Patient felt warm; urine passed rich in hemoglobin.
At 12:45 p. m., 102 degrees.
At 1:20 p. m., 100.2 degrees.

The arterial blood pressure was 146 mm. Hg., systolic pressure, before, during and after the attack.

The diastolic arterial pressure during the corresponding periods was 95. The chill and fever did not, therefore, modify the systolic or the diastolic blood pressure.

During the febrile period at 12:50 p. m. blood drawn into a syringe containing a small amount (2 per cent. of a 1 per cent. solution) of potassium oxalate and immediately centrifuged showed a distinctly pink serum which gave only the absorption bands of oxyhemoglobin to spectroscopic examination. Blood drawn and treated in the same manner before the patient's foot was placed in the cold bath revealed a normal serum. A few days later a cantharides plaster was applied to the arm. Three hours later when the serum was expected to accumulate in the underlying blister an attack of hemoglobinuria was induced. This serum was pink and showed the oxyhemoglobin bands under the spectroscope. A cantharides blister during an interim showed straw-colored serum.

The leucocyte count before an induced attack was 6,000; at the end of the chilly period the leucocyte count was 17,000 and was due to an increase of the polymorphonuclear cells. The leucocyte count made on March 7 was as follows:

At 9:00 a. m., before the chill, = 6,000
At 11:30 a. m., after the chill, = 17,000
At 1:00 p. m., = 15,000
At 4:00 p. m., = 11,000

During this attack the red cells were reduced 700,000 per c. mm. An ophthalmoscopic examination during one of the attacks revealed nothing abnormal in the eye-ground.

During the attacks the urine was colored a dark chocolate hue and showed nothing more than the presence of albumin, hemoglobin and casts of blood pigment.

From the above observations it was apparent that exposure to cold caused hemoglobinemia which was well pronounced before the febrile period. It is also clear that the rigor is associated with a slight lowering of the body temperature, and that the rise in temperature marks the cessation of the chill, which is unlike the relations between rigor, temperature and sense of warmth in the course of infectious diseases with which we are familiar.

The rise in temperature is associated with a pronounced polymorphonuclear leucocytosis.

The second patient B, an American, 25 years old, was admitted to Lakeside Hospital April 18, 1908. This patient was much more sensitive to cold than patient A. Without any history of illness or infection of any kind which could have any bearing on his present illness, B commenced having paroxysmal attacks of hemoglobinuria identical in character with those of A, eighteen months before admission to the hospital. As in A, the physical examination revealed absolutely nothing of an abnormal character. During warm weather he is perfectly comfortable, but if the thermometer is as low as 10 C., he is liable to an attack. He is particularly sensitive to a cold, moist wind, and has had as many as three attacks in one day. This patient gave no history of chilblains as did A, but at the conclusion of an attack there would be on the trunk and arms several small macules about one-sixteenth of an inch in diameter, in the middle of which a small blister would rise, from which the serum would escape during the febrile period and leave a very minute particle of desquamating epithelium apparent in the middle of the red areola. By the following morning all traces of the skin manifestations were gone.

The observations made on patient A were repeated on patient B. B suffered from a malady identical in character with that of A; the only essential difference being one of degree.

STUDY OF THE SERUM IN THESE CASES.

We then undertook a study of the serum of these patients from the standpoint of the side-chain theory, with the following results:

Although we were unable to find any organism in the patient's blood, either during the attacks or in the interims, it was clearly apparent that cold was essential for the hemolytic activation of the patient's blood.

Our first experiments consisted in attempting to activate the serum of these patients by exposing it to a low temperature, then warming the serum to 37 degrees C., and adding washed red-blood cells obtained from other patients with normal blood. After repeated trials with serum of these hemoglobinuric patients obtained by venous puncture and from blister serum (all of which were unsuccessful as long as the red cells were added to the serum when warm), we then chilled the serum after red cells had been added. When this precaution was taken, and the mixture warmed, hemolysis was complete within a very brief period.

All the experiments gave the same results with sera A and B.

Hemoglobinemic serum chilled in a salt and ice mixture at 5 degrees C., for thirty minutes, then put in an oven at 37 degrees C. for one hour, and after the serum again attained body temperature the red cells from a normal blood which had been repeatedly washed in physiologic salt solution were added to the serum and again put in the oven. The result was negative. The experiment and results are expressed in the following formula:

H. S. + 5° C. for 30 minutes + 37° for 1 hour + R. B. C. = 0.

In the next experiment the red cells were added before the mixture was exposed to a low temperature, and as soon as the mixture was again warmed complete hemolysis occurred. This was apparent by the disappearance of all cloudiness and the mixture becoming a clear ruby-red solution with a marked diminution of the viscosity of the serum.

H. S. + R. B. C. + 5° for 30 minutes + 37° C. for 10 minutes = +.

The serum from patient B, with added red cells, was placed in the ice water for fifteen seconds, then put in a water bath heated to 56 degrees C. for ten seconds, at the end of which time hemolysis was complete.

The serum from patient A required a longer exposure to cold to produce hemolysis, which is quite consistent with the comparative clinical histories of the two men. B was much more sensitive to cold than A.

Accidentally we discovered that if the suspension of red cells in the serum of B was placed near a 32-candle-power incandescent electric lamp after having been exposed to cold, hemolysis occurred very promptly.

If a suspension of red cells in the serum was placed in a water bath at 15 degrees C. for five minutes and then exposed to the rays of the lamp, which registered 25 C. on a thermometer placed beside the test-tube, hemolysis was prompt and complete, that is, it occurred at the end of eight minutes.

A drop of the suspension of red cells in serum from B was placed under the microscope after the mixture had been exposed to cold. The rays of an Abbé condenser supplied sufficient heat to cause rapid hemolysis, which could be observed under the microscope. Many cells disintegrated by fragmentation and many faded from view as the hemoglobin content was dissolved out of the stroma. The entire field was then filled with fragments of red cells which would certainly have been mistaken for blood platelets so far as their morphology was concerned.

If the suspension of red cells in serum A or serum B were exposed to a low temperature for hours, no hemolysis occurred until the mixture was again warmed.

The reduction in temperature necessary in the laboratory tests to procure activation of this lytic serum gives a very striking suggestion of the radiation of heat from the surface of the body and the subsequent warming of the blood from the surface, as it again meets the visceral blood, and it also illustrates the maintenance of the internal heat by metabolism.

If serum from normal blood was substituted for the lytic serum, and washed red cells from either A or B were substituted for the normal red cells employed in the former experiments, hemolysis did not occur.

This showed that the lytic principle was contained in the serum, and that hemolysis did not result from a diminished resistance of the patient's red blood cells.

If to a suspension of washed red cells (5 per cent.) in 0.5 c.c. normal serum, 0.03 c.c. of serum B was added it was found to be the minimum proportion of lytic serum necessary to cause hemolysis. So it may be said that approximately 6 per cent. of serum B added to normal serum was required to cause hemolysis of 5 per cent. suspension of red cells.

Thus far it is evident that cold (15 degrees C.) is essential for fixation of the lytic principle to the red cells, and that a temperature of 25 C. is necessary for the accomplishment of hemolysis.

This behavior of the lytic principle strongly suggests the applicability of the side-chain theory to this instance of hemoglobinuria.

In an article by Donath and Landsteiner[1] we find they had the same experience as we had in producing hemolysis *in vitro* with the serum from a case of paroxysmal hemoglobinuria, and, although they attempted to prove the applicability of various steps in the side-chain theory, they failed to reactivate the serum after it had been inactivated by heat at 56 degrees C. for ten minutes.

If the serum is heated to 56 C. for twenty-five minutes all attempts to procure hemolysis by exposure to cold and then to 37 C. are futile. This shows, of course, that there is an unstable substance essential for hemolysis which answers to the complement of Ehrlich's theory. It now remains to be shown that there exists also a stable substance which serves as the amboceptor between the complement and the red cells. The first step to prove this point requires a successful reactivation of the serum. If done by the usual method employed in hemolytic experiments as tried by Donath and Landsteiner the result is negative.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 5° C. for 30 minutes + 37° C. for one hour.

Now if the normal serum be added and the mixture is placed in the thermostat for many hours no hemolysis follows.

Inasmuch as a low temperature was required to procure fixation of the amboceptor to the red cell it seemed probable that reactivation experiments had hitherto failed because a low temperature was not employed in fixing the complementophilic end of the amboceptor to the haptophore of the complement. The following reactivation experiment proved successful.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 0.25 c.c. of normal serum + 5° C. for 15 minutes.

The mixture was then warmed to 37 degrees C. and hemolysis followed immediately.

Thus it is apparent that cold is essential for the fixation of both the cytophilic and the complementophilic ends of the amboceptor.

The foregoing experiments prove the existence of two essential factors in the lytic principle of the serum, one of which is unstable and is rendered inactive by heat and is present in all human sera; the other factor is more resistant to heat and is present only in the serum of patients in whom exposure to low temperature produces hemoglobinemia.

Eason[2] in his experiments on the serum of a patient with paroxysmal hemoglobinuria by a different procedure showed practically the same point, although he failed to recognize the need of a low temperature to secure union between the complement and amboceptor. In his experiment red blood cells were added to the patient's inactivated serum and the mixture exposed to ice-water for half an hour. After the mixture was removed from the ice-water bath the complement from normal serum was added, how long after he does not state, but from our results the mixture must have been cold when the complement was added or hemolysis would not have occurred when the whole mixture was put in the brood oven.

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[1] Donath and Lundsteiner: München. med. Wchnschr., 1904, li, 1590.

[2] Eason: Jour. Path. and Bacteriol., 1906-7, xi, 169.

If we are permitted to use the terms amboceptor and complement as applied to these two factors contained in the lytic serum it is incumbent on us to show that the union between the amboceptor and red cell is a biochemic union and one that can not be destroyed by washing the cells with physiologic salt solution after red cells have been exposed to cold in the presence of the inactivated serum from patients A and B respectively. At this period in our work we found that the oxalate serum did not differ from the serum which was procured by letting the serum separate out of the blood on standing. And as the serum could be procured more promptly and in larger amounts by centrifuging the oxalate blood, hereafter when the term H. S. is employed we shall mean hemoglobinemic serum to which 2 per cent. of 1 per cent. solution of potassium oxalate has been added.

The following is an experiment to show the fixation of the amboceptor which proved negative because the mixture was not exposed to a low temperature after the complement from a normal serum was added.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 5° C. for 1 hour.

The mixture was centrifuged and the supernatant fluid drawn off; the red cells were washed three times with large amounts of an isotonic salt solution. We then had presumably the red cells with the amboceptor fixed to them and clear of any of the excess of amboceptor which might have clung to the cells from the inactivated H. S.

If normal serum was now added to these (red cells + amboceptor), and the mixture placed in an oven at 37 degrees C. no hemolysis followed. In subsequent experiments, however, the mixture of (red cells + amboceptor) + normal serum was exposed to a temperature of 5 degrees C. for fifteen minutes and then hemolysis occurred as soon as the mixture was again warmed to 37 degrees C. Here again we have proof of the need of cold to procure fixation of the complementophilic end of the amboceptor to the haptophore of a normal serum.

The following experiments were made to show how the amboceptor could be exhausted from the lytic serum.

To 1 c.c. of inactivated H. S., five drops of a 10 per cent. suspension of washed red cells were added. The mixture was exposed to 5 degrees C. for one hour, then centrifuged and the supernatant serum drawn off. To the supernatant serum, red cells were again added and then 0.25 c.c. of normal serum added to the mixture. This mixture was exposed to cold for fifteen minutes and warmed to 37 degrees C. Hemolysis followed immediately, but it was not so pronounced as in our other reactivation experiments.

If to 1 c.c. of inactivated H. S. five drops of a 10 per cent. suspension of red cells were added, the mixture exposed to 5 degrees C. for one hour and then centrifuged, the supernatant serum again exposed to 5 degrees C. for one hour with five drops of a 10 per cent. suspension of red cells again added to the serum, and then centrifuged, the supernatant serum could not be reactivated.

Thus we have shown that if in two stages, ten drops of a 10 per cent. suspension of red cells be added to (1 c.c.) the serum and exposed to cold for one hour each time, the amboceptor can be exhausted from the inactivated hemoglobinemic serum.

From a number of such experiments we learned that if the serum with red cells was exposed to cold less than one hour we could not procure fixation of the amboceptor.[3] Thus far we have shown that the hemoglobinemic serum contains two factors, one unstable and capable of being inactivated by exposure to a temperature of 56 degrees C. for twenty-five minutes and is a factor which is common to all human sera and answers to the complement of Ehrlich.

The other factor is found only in the hemoglobinemic sera and is resistant to 56 degrees C. for twenty-five minutes. This factor answers to the amboceptor of Ehrlich and can be fixed in a biochemic union to the red cells and can be exhausted from the hemoglobinemic sera if a sufficient number of red cells be suspended in the serum and the mixture exposed to a low temperature for one hour.

In watching hemolysis take place under the microscope and seeing the extreme rapidity with which hemolysis occurred in the test-tubes we were impressed with the striking similarity between this hemolysis and the hemolysis which occurs when small amounts of ether are added to a test-tube of isotonic salt solution with red cells in suspension.

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[3] Eason (Jour. Path. and Bacteriol., 1906-7, xi, 169) was able to procure fixation of the amboceptor after one-half hour exposure to cold. He was also able to exhaust the amboceptor by one-half hour exposure to cold.

The natural deduction from such observations was that the lytic principle of the serum attacked the lecithin, cholesterin or some other lipoid of the red-cell stroma. If this were the case, then an excess of a mixture of lecithin and cholesterin in the serum would satisfy the avidity of this lytic substance and protect the red cells from destruction.

The following experiment was made to show this point:

An emulsion of lecithin (Merck) in normal salt solution and a mixture of cholesterin (Merck) in normal salt solution were made. Both mixtures were very thick. Three drops of each were added to 0.5 c.c. of H. S. and the mixture permitted to stand for one hour. Washed erythrocytes were added to the mixture and the whole mass exposed to 5 degrees C. for thirty minutes and then put in the oven at 37 degrees C. for twelve hours. No hemolysis followed.

We found then in trying lecithin and cholesterin separately that lecithin did not in the least inhibit hemolysis, but that cholesterin always prevented hemolysis even in the slightest degree when present to the extent of 5 per cent. or more.

It remained to be shown how cholesterin exercised this inhibitory effect on hemolysis—whether cholesterin exercised merely a negative reactive influence or formed a union with the complement or with the amboceptor.

To the hemolytic serum an emulsion of cholesterin in normal salt solution was added, and the mixture permitted to stand in the oven at 37 degrees C. for one hour. The mixture was then centrifuged and the clear supernatant serum removed. To this clear serum cells were added and the suspension of cells in the serum put in the cold bath at 5 degrees C. for one hour. The mixture was then put in the oven at 37 degrees C. and at the end of twelve hours there was no hemolysis.

From this experiment we are permitted to assume there was a deflection of either the amboceptor or the complement. Unlike the behavior of the receptors of the red cells and the amboceptor, however, we found by repeated experiments that a low temperature was not favorable to anchorage of the cholesterin.

Cholesterin protected the red cells when 5 degrees C., 22 degrees C. and 37 degrees C. were employed, but the best protection seemed to be afforded when the cholesterin was in contact with the serum at 37 degrees C., so the affinity between the lytic principle of the serum and cholesterin was not identical in character with the linking of the amboceptor to the red cells.

The following experiments were then made to show whether the amboceptor or the complement was deflected:

One c.c. of the serum was inactivated by heating it at 56 degrees C. for twenty-five minutes. To this inactivated serum cholesterin in excess was added and the mixture permitted to stand at 37 degrees C. for one hour. The mixture was then centrifuged and the supernatant serum was clearer than the original unheated serum. We then assumed if cholesterin was fixed in this inactivated serum it must be fixed to the amboceptor.

To this clear serum washed erythrocytes were added and the suspension was exposed to 5 degrees C. for one hour. The mixture was then warmed to 37 degrees C. and 0.4 c.c. of normal serum was added and the mixture again chilled at 5 degrees C. for one hour. The mixture was then put in the oven at 37 degrees C. and in thirty minutes hemolysis was complete.

Therefore, treating the inactivated serum with cholesterin did not prevent anchorage of the amboceptor to the red cells.

The following method was then employed to show whether cholesterin deflected the complement or not in a reactivation experiment:

One c.c. of H. S. was heated at 56 degrees C. for twenty-five minutes. Red cells were then added and the mixture chilled at 5 degrees C. for one hour to fix the amboceptor. Cholesterin was then added to the mixture after it stood in the oven at 37 degrees C. for twenty minutes. Normal serum was then added to the mixture which was chilled at 5 degrees C. for thirty minutes. The mixture was then warmed and permitted to stand until the following day, but there was no hemolysis. This experiment shows that cholesterin acts by deflecting the complement.

Early in our experiments on these patients we tried calcium lactate as a remedy against hemolysis in both patients. They were given sixty grains a day over a period of two weeks, but at the end of that period the patients responded to cold as before and the hemolysis *in vitro* was unaffected. Nor did calcium lactate inhibit the hemolysis *in vitro*. After our experiences with cholesterin in the laboratory we administered cholesterin to these patients per os ten grains three times daily dissolved in olive oil. After ten days' trial of the cholesterin treatment we found that hemolysis *in vitro* was unaffected in both patients. The weather during this period was very warm, so neither patient had an attack, and although neither patient objected to repeated venous punctures for obtaining blood, they did not wish to expose themselves to an attack of hemoglobinuria by exposure to a cold foot bath. So whether the cholesterin therapy may offer protection against attacks due to exposure to cold or not remains undecided.

We make this statement in view of the experience which Widal and Rostain[4] had with their patients, on whom they were able to confer passive immunity by means of an antihemolytic serum. Although the patients of Widal and Rostain enjoyed immunity from attacks on exposure to cold, their sera was as actively hemolytic *in vitro* during this period of immunity as before.

We repeated the experiment of Widal and Rostain in procuring an antihemolytic serum from a rabbit by treating the animal with normal human serum.[5]

The rabbit was given four intraperitoneal injections during a period of three weeks. The amounts of normal serum used at each injection were 5 c.c., 15 c.c., 12 c.c. and 12 c.c. respectively.

To inhibit the lytic action of these patients' sera on red cells we found it necessary to employ about 12 per cent. of the inactivated immune rabbit's serum added to the serum of patients A and B. Normal human serum was hemolytic to the rabbit's washed red cells, but the sera from our patients was more strongly hemolytic than normal human serum.

In tube A was placed 10 c.c. of normal human serum and in tube B was placed 10 c.c. of hemoglobinemic serum from patient B. To each, i. e., A and B, were added 1 c.c. washed red cells from the rabbit. Both tubes were chilled at 5 degrees C. for twenty minutes and then both tubes were put in water (55 degrees C.) for fifteen seconds. Both tubes showed hemolysis immediately, but the hemolysis in tube B was more complete than in tube A. We also found that normal human serum completely laked the rabbit's cells at 37 degrees C. in forty-five minutes without the previous exposure to cold.

The treated rabbit's serum also completely laked normal human red cells at 37 degrees C. in forty-five minutes without previous use of cold.

To test the antihemolytic property of this "sensitized" rabbit serum it was, of course, necessary to inactivate the serum at 56 degrees for twenty-five minutes.

We then found it was necessary to add as much as 12 per cent. of the inactivated rabbit's serum to the serum of patient B before hemolysis could be completely prevented. The antihemolytic property of our rabbit's serum was not so highly developed as in the rabbit of Widal and Rostain, probably because the rabbit was treated for a shorter time than was the rabbit in the hands of Widal and Rostain.

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[4] Widal and Rostain: Compt. rend. Soc. de biol. de Paris, 1905, 1, 321.

[5] Eason (Jour. Path. and Bacteriol., 1906-7, xi, 203) employed the serum of a patient suffering from paroxysmal hemoglobinuria for the same purpose. Any human serum serves the same purpose.

Widal and Rostain found that they could confer a passive immunity on their patients by subcutaneous injection of 25 c.c. of the inactivated serum from the sensitized rabbit. This immunity against cold lasted for only ten days. But during the immune period the lytic property of their patients' serum *in vitro* was undiminished.

This antihemolytic serum of the sensitized rabbit inhibits the hemolysis if it is added to the mixture of red cells and lytic serum after exposure to cold.

The protection from this serum is by virtue of deflection of the complement and is not due to antiamboceptor.

The question of etiology arises in relation to these experiments in hemolysis in the following manner:

1. Is the lytic property of these patients' sera due to a want of the normal antihemolysin which is presumed to be present in the sera of all normal animals?

2. Does the lytic principle of these sera partake of the character of a catalytic agent or a ferment?

3. Or is the lytic substance a biologic product of some form of infection which thus far has defied our attempts at detection?

If the first hypothesis were tenable we should expect to find hemolysis inhibited by the addition of inactivated normal human serum. This, however, is not the case. If inactivated normal serum is added to the fresh lytic serum in equal amounts and the mixture permitted to stand, either at a low temperature or at 37 degrees C. for an hour before red cells are added, hemolysis results after the mixture is exposed to cold just as in the original experiment.

The second hypothesis is not tenable because the amboceptor can be readily exhausted from the inactivated lytic serum by the exercise of its function of fixation to the red cells. A catalytic agent would not be sacrificed in such measured quantities by the exercise of hemolysis.

The third hypothesis does not admit of disposal. It is true that these patients are in good health as long as they are not exposed to cold, and the fact that they have hemoglobinemic fever can not be regarded as the direct effect of some organism. The abundance of cell shadows which must exist in the plasma of these patients after hemolysis occurs is quite sufficient to account for their fever. But patients may have infections without an elevation of temperature, and that, too, when organisms can be cultivated from their venous blood.

We had a patient in our wards at Lakeside Hospital during the past year who was a good example of an afebrile infection.

A young man 20 years old presented all the clinical signs of Hanot's type of hypertrophic biliary cirrhosis of the liver with splenic tumor and slight icterus. The patient remained three months in the ward and during that time a careful watch of his temperature never detected a rise above 99 degrees F. From the fluid gained by punctures of the spleen and the liver and from blood obtained from the vein of his arm we were able to cultivate a large motile bacillus with many characteristics of the common colon bacillus. It is true that the patient was ill, but he was not ill on account of his infection, but on account of his diseased liver and spleen. With such experiences in mind it does not require a great flight of imagination to conceive of an infection of some kind being the underlying cause of our patients' hemoglobinemia.

Now, if such were the case we should expect to find some evidences of an antibody in the blood of the patient who has had his disease five years and who is less sensitive to cold than the other patient who has had his disease only one and a half years.

With this idea in view, inactivated serum from patient A was added in equal amounts to the fresh serum of patient B and inactivated serum from patient B was added to the fresh serum from patient A in equal amounts. These mixtures were permitted to stand one hour before red cells were added, but hemolysis resulted after the usual procedure of exposing the mixtures to 5 degrees C. and 37 degrees C. as in our earlier experiments.

As the matter at present stands we are justified only in saying that the hemoglobinemia which follows exposure to cold is due to some biologic product in the plasma which in its behavior admits of the demonstration of every step in hemolysis as expounded by the side-chain theory of Ehrlich.

In conclusion it gives us great pleasure to express our gratitude to Dr. J. J. Macleod, professor of physiology in Western Reserve Medical School, for valuable suggestions and consultations during the progress of our work.

Rose Building.

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AMERICAN MEDICAL ASSOCIATION, ONE HUNDRED AND THREE DEARBORN AVENUE.
CHICAGO.

SERUM TREATMENT OF EPIDEMIC CEREBROSPINAL MENINGITIS.*

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Previous to the work of Flexner in this country and that of Kolle and Wassermann and Jochmann on the continent, little had been accomplished in the production of a serum curative for epidemic cerebrospinal meningitis. The experiments of Bonhoff and of Lipíerre, while suggestive of results, were too incomplete and unsatisfactory to warrant conclusions that they were working with a serum of protective and curative value. They were unable to reproduce the disease experimentally in animals in a form simulating that disease in human beings, and there is some doubt as to whether their control animals, for the most part guinea-pigs, died from toxemia or from infection.

THE SERUM.

As a result of the epidemic of cerebrospinal meningitis which devastated greater New York during the winter of 1904 and spring of 1905, in which there were about 4,000 cases with 3,429 deaths, Dr. Flexner, as a member of a commission appointed by the Health Department of New York City, undertook an experimental investigation of epidemic meningitis, with the result that he proved conclusively that this type of cerebrospinal meningitis could, by direct inoculation into the spinal canal, be transmitted to monkeys in a form closely resembling that found in human beings. Furthermore, he was able to produce an antidotal serum for the meningococcus which, when inoculated in certain quantities at the same time as an otherwise fatal dose of living cultures of the meningococcus, would in almost all cases prevent the disease from terminating fatally in monkeys. He also could save monkeys inoculated with a lethal dose of living cultures of meningococcus when serum was injected into the spinal canal not later than six hours afterward.

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* Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-ninth Annual Session, held at Chicago, June. 1908.

Serum used in this series of cases was furnished by Dr. Flexner and was in brief made as follows: Horses were injected first subcutaneously, then intravenously, with gradually increasing doses of living meningococci. Later subcutaneous injections of an autolysate were used in gradually increasing doses. Many different strains of meningococci were employed in preparing the living culture and the autolysate for inoculation. After months have elapsed the horse was bled, the serum collected and bottled ready for use.

SERIES OF CASES TREATED.

The serum was first used systematically by me in a series of cases beginning April 2, 1907, at Castalia, Ohio, where an epidemic of cerebrospinal meningitis had created such havoc that half the population of the village of 600 inhabitants had fled in terror. Between the months of January and April, 1907, 18 cases of meningitis developed. Of the 18 patients, 12 died and 6 recovered, a mortality of 66.7 per cent., a recovery of 33.3 per cent. Serum was used in three cases. All the patients recovered. In the 15 cases in which the serum was not used, 12 patients died and 3 recovered, a mortality of 80 per cent., and recovery of 20 per cent.

In the first few cases treated, from 5 to 10 c.c. of serum was injected at a dose, but wider experience showed it to be safe to use large amounts, and then from 15 to 30 c.c. was used at one injection, provided that much fluid was withdrawn. These injections were usually repeated at daily intervals until acute symptoms subsided and the spinal fluid became clear. In some instances two injections were made daily. When the meningeal symptoms disappeared and the temperature subsided, the further use of the serum was discontinued until a rise in temperature or increase in meningeal symptoms made it seem advisable to again employ it.

Altogether, the serum has been employed by me in 32 cases. Of the 32 patients one is still in the acute stage of the disease and can not be considered in this report. Of the 31 cases to be considered, in 30 the diagnosis was confirmed by finding the characteristic Gram-negative diplococci in coverslip preparations, and in almost all cases cultures were positive. In one case, clinically typical of cerebrospinal meningitis, with marked petchial eruption, only a few drops of bloody serum was obtained by lumbar puncture, from which nothing definite was made out. The boy's mother, however, had nursed a fatal case of this disease two weeks previous to the onset in him.

That these cases were not mild ones but of marked severity and a severe test of the therapeutic value of the serum is made evident by the fact that when serum was administered 17 of the patients were comatose, 3 unconscious and wildly delirious, and 12 semiconscious or conscious with great irritability.

Many of these cases were seen in the outlying and poor districts, where it was impossible to obtain as complete records in regard to temperature, pulse and respiration as desirable, though as a rule the records are complete enough to enable one to follow the progress of the cases satisfactorily. A good proportion of the cases were under constant observation at the various hospitals in Cleveland.

Eleven of the 31 patients died and 20 recovered—a mortality of 35.5 per cent. and a recovery of 64.5 per cent. Four of the comatose patients were moribund at the time of the administration of the serum, dying within a few hours. Three of the cases in which the patients were moribund were of the fulminating type and were seen forty-eight or less hours after onset. A fifth was a chronic case of nearly four months' standing, in which the patient was blind, deaf, comatose and a mere breathing skeleton at the time of administration of the serum. In a sixth case of thirty-nine days' duration before serum was employed, chronic hydrocephalus had already developed. Subtracting these 6 cases, manifestly unfair tests of the treatment and hopeless so far as serum therapy is concerned, there would be 25 cases with 5 deaths, a mortality of 20 per cent. and a recovery of 80 per cent.

Twenty-four cases were treated ninety-six or less hours after onset. Of these patients 16 recovered and

8 died, a mortality of 33.3 per cent. and recovery of 66.7 per cent. The four moribund patients were included in this group. Subtracting them, there would be 20 cases with 4 deaths and 16 recoveries, a mortality of 20 per cent. and recovery of 80 per cent.

Eighteen cases were seen seventy-two hours or less after onset of symptoms. Fourteen of the patients recovered and there were 4 deaths, a mortality of 22.2 per cent. and recovery of 77.7 per cent. Three of the moribund patients fell within this group. Deducting these, there were 15 cases with 1 death, a mortality of 6.6 per cent. and recovery of 93.4 per cent.

Thirteen cases were seen forty-eight hours or less after onset of symptoms. Nine of these patients recovered and 4 died, a mortality of 30.7 per cent. and recovery of 69.3 per cent. Three of the moribund patients were included in this group. Subtracting these, we have 10 cases with 1 death, a mortality of 10 per cent. and recovery of 90 per cent.

Five cases were seen twenty-eight hours or less after onset of symptoms. All of these recovered, a recovery percentage of 100 per cent.

Eleven of the 31 cases developed in children under 5 years of age. Six of these recovered and 5 terminated fatally, a mortality of 45.5 per cent. and recovery of 54.5 per cent. In these 5 cases which terminated fatally 4 patients died of chronic hydrocephalus, late in the course of the disease, and a fifth case died during the acute stage of the disease.

The average duration of the disease in cases of recovery seen twenty-eight hours or less after the onset of symptoms, when treated with the serum, was twelve days; above twenty-eight hours and including forty-eight hours, nineteen days; above forty-eight hours and including seventy-two hours, forty-nine days. As most of the cases seen later than seventy-two hours died, a satisfactory statistical chart of cases recovering can not be compiled at this time.

Fever terminated by crisis in 11 cases and by lysis in 9 cases. In one case the temperature was normal at the time of administration of serum and afterward.

Of the 11 fatal cases 4 patients died from chronic hydrocephalus, and 4 were moribund at the time of administration of the serum. One patient in the acute stage of the disease died shortly after the administration of the serum, and in this case there is a possibility that the severe chill, cyanosis and rise in temperature to 106 degrees was produced by the bactericidal action of the serum on the numerous meningococci present and liberation of more endotoxins than could properly be taken care of by the patient. In one case death occurred in the chronic stage of the disease nearly six months after onset. Acute dilatation of the heart and pulmonary edema produced death during the acute stage of the disease in the last case.

In this series of cases the youngest individual was 3 months old and the oldest 28 years of age.

The onset was with marked gastrointestinal symptoms in six cases, marked diarrhea and vomiting being present.

Petechial eruption alone was present in 11 cases and associated with hemorrhages into the skin in 3 additional cases. A petechial eruption associated with herpes labialis was present in one case. A petechial, hemorrhagic and herpetiform eruption were all present in one case. A petechial eruption associated with erythematous eruption was present in one case. An erythematous eruption only was present in two cases. A macular eruption was present in one case. Mottling of the skin and herpes labialis were associated in one case. In two cases mottling alone was present. Nine cases were unassociated with skin eruptions. Surprisingly few patients had herpes.

In two cases well-marked urticarial eruption developed as a result of the administration of the serum. In one of these cases the eruption came on fifteen days after the injection of the serum, and in this case practically all the serum administered was given subcutaneously. In the second case the urticarial eruption developed one week after 35 c.c. of serum had been administered intraspinally, the child being perfectly well in other respects at this time.

Sequelæ were present in three cases. In Case 1 a left-sided foot drop developed, which is gradually improving. In Case 15 slight impairment in hearing persists. In Case 31 a marked suppurative arthritis of the left knee is rapidly clearing up under treatment by aspiration and injection of serum directly into the joint.

Examination of the spinal fluid in all cases showed the polymorphonuclear neutrophilic leucocyte to be the predominant cell with varying numbers of endothelial cells present. The largest number of endothelial cells found were in the fluid obtained from Case 31, in which diplococci were very few and hard to find. In many cases these endothelial cells were phagocytic for meningococci and not infrequently contained polymorphonuclear leucocytes in various stages of disintegration. In a very few cases with a diminution of turbidity of the spinal fluid an increase in lymphocytes was noted, and in one case, well along in the course of the disease, differential count showed 98 per cent. of lymphocytes. As a rule the neutrophilic leucocytes are very much in excess, and as the fluid becomes clearer, while they diminish in numbers, differential count still shows them to be approximately 90 per cent. or more of all cells. The number of diplococci present in the spinal fluid seems to have no bearing on the severity of the clinical symptoms. In some cases in which there was most marked petechial eruption, coma and meningeal symptoms, it was difficult to find organisms. Occasionally organisms could be found only after cultures had been made or after incubation for twelve hours of the original spinal fluid. On examination of such incubated spinal fluid one often finds very numerous intracellular and extracellular meningococci, which can then be cultivated more readily.

In most cases in which recovery takes place after the injection of serum the spinal fluid progressively becomes clearer and diminished in amount. In several cases, especially those in which few or a moderate number of meningococci were found, these could not be cultivated subsequent to the injection of serum, though they grew readily at first. In such cases, as a rule, the diplococci do not stain well. At other times growths could be obtained until after the second or third dose of serum had been administered, and occasionally when considerable amounts had been given after longer intervals of time had elapsed. In cases in which the micro-organisms, both intracellular and extracellular, are present in exceedingly large numbers, it has been my experience that the prognosis is not so good, even though the patient may present no worse symptoms clinically than other patients from whom fewer organisms have been obtained. In such cases rises in temperature following the administration of serum have taken place several times, and in one case in particular I could not help but feel that more endotoxins had been liberated than could be properly taken care of by the antitoxin properties of the serum or by the patient himself. In such cases I should feel like giving a small amount of serum intraspinally with frequent repetitions and larger amounts subcutaneously. Or, if large amounts be used intraspinally they should be sufficiently large (for example, 30 c.c. or more) to provide antitoxin properties enough to neutralize the endotoxins liberated. It should be advisable, also to administer considerable serum subcutaneously.

Absence of fever does not mean necessarily a betterment in condition, as frequently a very purulent spinal fluid is withdrawn in cases with normal temperature when seen.

In several instances in which it has been difficult to find meningococci on first puncture and in which cells containing the meningococci contained very few, after the administration of serum and subsequent withdrawal of fluid, I have repeatedly found cells packed with meningococci, though possibly there were no more phagocytic cells than on first examination. This would indicate that opsonins played a definite part in the process of immunization. The poor staining of the meningococci seen after the use of the serum would seem to point to definite bactericidal properties in the serum.

Some of the cases presented features of unusual interest, and I shall breifly mention them.

In Case 2, which was almost in the third week of the disease, the disease terminated abruptly after the withdrawal of fluid and injection of serum.

Case 8 was interesting because a young man desperately ill was cured by subcutaneous injections of serum, only 5 c.c. having been given intraspinally. The subcutaneous method was used because frequent attempts to withdraw fluid by puncture were unsuccessful, only a few drops of bloody serum being obtained.

In Case 12 the question arises whether the liberation of endotoxins following the injection of serum had anything to do with the appearance of a marked chill, cyanosis and rise of temperature to 106 degrees with death shortly afterward.

In Case 13 puncture and injection of serum was made in less than two hours after development of meningeal symptoms, with a result that the disease was promptly arrested in its progress in spite of the fact that there was much pus present and fairly numerous meningococci.

Case 17 is of interest because sharply staining Gram-negative intracellular diplococci were found in the spinal fluid at the time of puncture, approximately four months after onset. Cultivation of these were unsuccessful.

Patient 19, a child 7 months old, was discharged apparently well sixty-one days after the onset of the disease, but was readmitted seventeen days after the discharge on account of convulsions associated with twitching of the right side of the face and of the extremities on the right side. There had been four such attacks, beginning six days after discharge from the hospital, and the child was admitted the second time during the fourth attack, which lasted five hours. This attack was promptly checked by lumbar puncture and the withdrawal of 35 c.c. of perfectly clear fluid. No further attacks have since developed.

In Case 23 it was difficult to tell what marked the onset of the cerebrospinal meningitis; whether an acute process due to the meningococcus was engrafted on a more chronic obscure trouble, or whether from the first the condition was due to a meningococcus infection of unusual onset.

In Case 25 a condition of hydrocephalus in which large amounts of clear fluid were obtained by puncture, following the subsidence of the acute meningeal symptoms and which gave every evidence of becoming chronic, eventually subsided completely and the child remains well at the present.

The feature of particular interest in Case 29 was the direction followed by the aspirating needle in getting into the spinal canal. Attempts to get the needle in by the direct method in the mid-line, or by the up-an-in method, starting slightly below the mid-line, resulted negatively, and fluid was obtained only when the needle was directed down and out, the needle being inserted below the mid-line between the third and fourth lumbar vertebræ. The child in this case was the subject of congenital lues, and no marked degrees of scoliosis was present.

Case 31 is the most interesting and important of the series.

Patient.—M. N., male, aged 28, was perfectly well on the early morning of May 16, 1908.

Onset of Disease.—At 9 o'clock in the morning, May 16, the patient felt sick and was seized with a violent chill. Temperature of 103 F., with a pulse of 100, and normal respirations developed about 3 o'clock in the afternoon of the same day. Patient was seen by Dr. Cheetham at 10 o'clock in the morning. No meningeal symptoms were present at this time. On the evening of the 16th headache developed and at 3 o'clock in the morning of May 17 the patient became wildly delirious and unconscious. At 5 o'clock opisthotonus, Kernig's sign, petechial eruption, with true hemorrhages into the skin, and general rigidity were present.

Clinical Course and Treatment.—May 17: The patient was brought to Lakeside Hospital at 2 p. m. At this time temperature was normal and the pulse 100. The patient was still wildly delirious and unconscious and required the efforts of three men to control him while chloroform was administered and lumbar puncture performed. Forty c.c. of quite turbid fluid was obtained and 30 c.c. of serum injected. Examination of this fluid showed a very rare and rather poorly staining intracellular diplococcus. Cultures were made and the original fluid incubated with the result that typical meningococci grew out in large numbers in the incubated fluid and a few colonies developed on artificial cultures.

May 18: The patient was better. Temperature was normal and pulse still about 100. There was still marked rigidity and Kernig's sign was present. Semiconsciousness was present, though at times patient could be aroused and made to answer questions intelligently. At 10 o'clock a second puncture was done and 25 c.c. of still turbid fluid was obtained. Fifteen c.c. of serum was given. Bacteriologic examination of this fluid gave results similar to those obtained at the time of first puncture, except that cultures failed to develop and even in the incubated fluid the meningococci did not increase in numbers. From this time on no further growth was obtained from the spinal fluid.

May 19: A third puncture was made and 45 c.c. of slightly blood tinged, but less purulent fluid was obtained. This came out under considerable pressure. Fifteen c.c. more of serum was injected intraspinally. The patient's mental condition was much brighter. Kernig's sign was still present but opisthotonus and muscular rigidity was less marked and the petechial eruption was beginning to fade. On this day the temperature went up to 100 with a pulse of 100, though the pulse was of a better character than at any time previous.

May 20: The temperature rose to 101, though the patient's condition was gradually improving as regards mental and meningeal symptoms. Lumbar puncture was performed and 25 c.c. of very slightly blood-tinged and still less purulent fluid obtained. Fifteen c.c. of serum was injected.

May 21: The patient's condition was so good that no lumbar puncture was made. Temperature was 101 F., pulse 90.

May 22: The patient's temperature continued to be 101, though all other symptoms were disappearing. Lumbar puncture was performed and 10 c.c. of quite clear fluid was obtained. Fifteen c.c. of serum was administered. The patient's mental condition was perfectly clear and except for very slight rigidity of the cervical muscles, and a still-present Kernig's sign, the meningeal symptoms had disappeared. Temperature still remained about 101 and continued at that point until May 25.

May 25: The temperature reached 103. The patient first complained of pain in the left knee joint. Examination of the joint demonstrated increased surface temperature, marked tenderness on palpation, and moderate bulging of the bursæ around the joint. Ice-bags were applied and the leg placed in a pillow splint.

May 26: The joint was more painful and hot and there was marked fluctuation present. The slightest motion caused excruciating pain. Aspiration was resorted to and 30 c.c. of thick purulent fluid obtained. Microscopic examination of this showed a very rare poorly staining intracellular diplococcus. No other micro-organisms were present. Cultures failed to develop even after incubation of the fluid. Fifteen c.c. of serum was injected into the joint through the aspirating needle.

May 27: The patient felt better, though there was still marked fluctuation present and great tenderness on motion. Temperature was 100. Aspiration was again resorted to with a result that about 40 c.c. of still very markedly purulent fluid was obtained. Fifteen c.c. more of serum was injected. Examination of the fluid removed resulted negatively insofar as cultures were concerned. When aspirating on this day lateral pressure was used in order that as much fluid as possible might be obtained. This was not done at the time of the first aspiration. The patient was told that if on the following morning he did not show more marked improvement surgical procedures would have to be resorted to.

May 28: The patient felt much better and there was less fluctuation, tenderness and surface temperature. Aspiration was again resorted to and 10 c.c. of distinctly less turbid fluid obtained, even though lateral pressure was exerted.

May 29: The temperature was perfectly normal and has remained normal since. There was no tenderness on palpation; surface temperature was normal, and patient could move the knee slightly. Aspiration resulted in the withdrawal of 2.5 c.c. of very slightly turbid fluid. Fifteen c.c.. more of serum was injected. Since this date patient has had no more tenderness on motion and pressure can be exerted on the knee joint without pain. Bulging has disappeared.

May 31: There was an angle of flexion amounting to 90 degress and there is every evidence that the joint will be cured with little or no limitation of motion.

Here, then, we have an illustration of the specific action of antiserum as applied to one of the most common complications of cerebrospinal meningitis, namely, arthritis, and that, too, of a suppurative character, with a result that so far is truly astonishing. Knowing the feeble powers of resistance on the part of the tissues of the knee joint in warding off infection, I confess that when I saw thick pus withdrawn by my syringe I felt that nothing but surgical intervention would save the joint, for I have little faith in the medical treatment of purulent joints. Having seen so often the beneficial results arising from the administration of this serum when injected intraspinally I saw no reason for not trying serum in this locality. While it is too soon to state definitely that there will be no limitation of motion, I feel confident, by reason of the rapid strides made so far, that there will be little, if any. So far as my personal knowledge extends—for I have not as yet had the opportunity of looking up the literature on the subject—this is the first case in which a suppurative knee has been treated by direct injection into the joint with a specific serum of undoubted bactericidal and antitoxic properties. This case, of course, opens up the problem of treating suppurative conditions of joints due to other micro-organisms with specific antidotal serum, provided, of course, that such sera can be produced for the given micro-organisms.

In conclusion, I can do no more than say that, so far as I myself am concerned, I have no doubt as regards the wonderful efficacy of Dr. Flexner's serum in the treatment of epidemic cerebrospinal meningitis, provided it is used on patients not moribund or on those in whom chronic hydrocephalus has not already developed. I confidently believe that statistical reports excluding these cases will show that our percentage of recovery will contrast favorably with our previously high percentage of deaths.

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A SIMPLE ASEPTIC SURGICAL TECHNIQUE.

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The observations recorded in this paper have for their object to establish an aseptic technique, at once simple and effective. They were all conducted under the same essential conditions of sterilization of the hands. Rubber gloves, sterilized by boiling, were used in every case. The conclusions rest upon 377 bacteriological examinations of the hands of the operator and his assistants, six in number, and upon the results obtained in 3500 operated cases.

The bacteriological investigations were conducted by my present First Resident Assistant, Dr. R. W. Elliott. The clinical records were compiled by my late First Resident Assistant, Dr. A. I. Ludlow, who was assistant in the hospital throughout the whole period during which the cases were under treatment. To insure accuracy the record of cases has been reviewed by the entire staff of assistants, resident throughout the period.

The work was suggested by the very interesting and valuable papers of Harrington, Monks, and Ochsner, published in the Transactions of the American Surgical Association, in 1904. A further incentive to the work came from the observations recently made in many European clinics that rubber gloves were not in common use. Strong objection was repeatedly offered to the use of gloves on the following grounds:

1. That the hand enclosed in a rubber glove for a considerable period was sure to develop abundant growths of bacteria.

2. That the puncture of the glove during operation would result in their escape into the field of operation.

3. That gloves were a serious hindrance in operating, and,

4. That they were too expensive.

The observations recorded would indicate, first, that rubber gloves are a great protection to both the surgeon and the patient, and, second, that a very simple technique may be absolutely relied upon to secure asepsis.

The following bacteriological observations, conducted in seven series, indicate sufficiently clearly the methods employed. The observations were made upon the first operations of each day, so as to represent the first sterilization of the hands.

Series A, B, and C were observations made upon the hands of the operator only, since his hands were usually encased in gloves when handling dressings and wounds and in making vaginal and rectal examinations, and thus were less liable to have on them infectious material than were the hands of the assistants, constantly working in the hospital, although the assistants, as a rule, wore rubber gloves while doing surgical dressings.

In Series D to G, cultures were made from the hands, both of the operator and his various assistants. The bacteriological observations are based upon cultures made upon numerous media—viz., plain, glycerine, glucose and hydrocele agar, bouillon, bouillon with glucose, and blood serum. Cultures taken from the hands of different assistants were usually made upon different media. The cultures were taken after removing the gloves at the close of operation, by rubbing a small swab of cotton between the fingers and about the bases and tips of the nails. In washing the hands the scrub brush was used not to exceed two minutes. It was used chiefly on the palms of the hands and about the tips of the fingers. The nail cleaner was used beneath the nails only, and never about the base of the nails. The backs of the hands and the arms were washed with soft soap, and were thoroughly rubbed with a towel or gauze. The scrub brush was never used upon the arms. A fresh, sterile operating gown was used in each operation, usually with sleeves reaching only half way from shoulder to elbow. Thus the operator's arms were bare from just above the elbow to the top of the glove, which reached about three inches above the wrist. This method was preferred to the long sleeve, since if by chance the arm touches anything outside of the operation, it is at once perceived by the operator. This is not true when the arm is covered by a long sleeve. Further, the gloved hands and arms are repeatedly cleansed in sterile water. No germicide is used either upon the wound or hands during operation.

Rubber sleeves, covering the entire arm were used only in operations where grave sepsis or abundant pus was present. They were employed only to protect the operator's arms. The operator, assistants, and nurses always wore caps, covering the hair and ears.

In the various series of observations following, record is made, (1) of the method employed for cleansing and (2) sterilizing the hands, (3) the time occupied by the various operations, (4) the nature of the operation, whether clean or septic, (5) the number of operations made for each period of time observed—*e. g.*, four operations occupying fifteen minutes each, etc., (6) the result—viz., whether the cultures were negative or fertile, and if fertile what growth was found. The results of the observations are as follows:

Series A. Cultures were all negative. The use of Harrington's solution, though showing sterile results in each observation, was unsatisfactory, since it caused irritation of the skin of the hands and arms, and rendered the nails brittle.

To overcome this difficulty the hydrochloric acid was omitted from the solution. This solution also proved to be irritating. The results obtained by this method, Series B, were equally successful with the former method. In Series A and B, after washing the hands in Harrington's solution, sterile water only was used in the gloves.

In Series C, the hands, after washing, were thoroughly bathed in 70 per cent. alcohol. The gloves were in sterile water when put on, no alcohol being used in the gloves. As a disinfectant alcohol proved inefficient. Out of 42 observations pyogenic organisms were found twenty times, or in nearly 50 per cent of the cases.

Puncture of the gloves in these cases might well have caused infection of the field of operation.

In Series D, E, F, and G, a solution of bichloride of mercury of varying strength was employed. The arms and hands were thoroughly washed with bichloride solution, and commonly both hands and arms were immersed in it, and the gloves were filled with the solution before being put on.

In Series D, F, and G, alcohol was used in cleansing the hands before putting on the gloves. In Series E no alcohol was used.

In the 285 observations made by the use of a solution of bichloride of mercury in the gloves, the hay bacillus was found once and the staphylococcus pyogenes albus was found twice. In each of these cases the growth did not appear until after several days, making it probable that it had slight virulence.

The object of using a solution of bichloride of mercury in the gloves is that its prolonged contact with the hands inhibits the development of bacteria. That it actually did this is evidenced by the fact that the cultures were taken from the hands after operations of all lengths, from ten minutes to one hour and forty-five minutes, and that they remained sterile.

The conclusions reached from these observations are:

1. By the use of Harrington's solution the hands may be rendered sterile, and will remain so in sterile gloves containing only sterile water. The writer found this solution irritating to hands and arms and undesirable on this account.

2. Hands thoroughly cleansed and later washed in alcohol develop the pathogenic bacteria when encased in gloves containing only sterile water. No experiments were made with gloves sterilized dry, and dusted with powder to facilitate putting them on. It seems, however, that bacteria would develop on hands encased in these gloves and moistened by perspiration, as certainly as on hands moistened by sterile water. While the dry glove dusted with powder might be used after disinfection with Harrington's solution, or one equally efficient, it would not seem safe under other conditions.

3. By washing the hands thoroughly and encasing them in

rubber gloves filled with a solution of bichloride of mercury, the hands develop pathogenic bacteria in so small a percentage of cases that the danger of sepsis is virtually destroyed.

As a result of the observations the method of sterilization determined upon is simply to wash the hands thoroughly, first with soap and water, and then with a solution of bichloride of mercury, of a strength of from 1:3000 up to 1:5000, and afterward to encase them in gloves containing the same solution. The writer uses 1:5000. Neither solution caused any irritation whatever to the hands of either the operator or any of his assistants. The use of alcohol in washing and disinfecting does not seem to be essential and has been discarded.

The clinical observations recorded in this paper are based upon 3500 operations. In the study of infection it has been thought wise to select only the clean cases. Cases infected before operation and cases in which prolonged drainage has been employed, as in cases of operation on the biliary tract, obviously should not be included. Also, cases which have died from shock, hemorrhage or other cause similarly unconnected with sepsis have been omitted as not bearing upon the question under discussion. All other clean cases operated upon within the period under observation are included.

The appended table of operations developing sepsis show the surgical number of the case, the diagnosis, operation, suture material, the number of days after operation when infection appeared, the degree of sepsis, and the final result. Cases of but a single stitch abscess are included in the table. In almost all cases the infection has been slight and of short duration. In one case of suture of a floating kidney the suppuration of the wound was general and prolonged.

In the series are 967 laparotomies. Of these 687 were clean and 280 were cases septic before operation. Of the total number of clean laparotomies stitch abscesses developed in 19 cases.

In the series of 2533 operations, other than laparotomies, 1452 were not septic before operation. In this series stitch abscesses developed in 39 cases and erysipelas developed in 1 case.

In the entire group of 2139 clean operations stitch abscesses developed fifty-eight times, or in about 2.25 per cent. of the cases. It is, of course, possible that some cases of infection may have escaped record, or have been overlooked in collecting the statistics, but the number of these must be very few, since the records are kept with unusual accuracy. The stitch abscesses developed in 35 cases in which chromic catgut was used. In 2 cases silk, in 1 silver wire, in 1 kangaroo tendon, in 3 silkworm gut were employed, and in the remainder the suture material used was not recorded. Since it has been the custom to use chromicized gut in uniting the fascia in all laparotomies, hernias, etc., there is little question that infection in these cases in which the suture material is not recorded, was associated with the use of chromicized gut. The chromic gut used for suture was usually No. 3.

In the entire series of 2139 operations upon clean cases, sepsis was the cause of death in only 2 cases.

The results obtained in the foregoing cases were, except for the experiments detailed in Series A, B, and C, secured under essentially the same conditions, so far as sterilization of the hands and the use of gloves were concerned. In approximately the first two-thirds of the series, the hands were washed in soap and water and then washed in alcohol before putting on the gloves in bichloride solution. No difference in the results has been observed by omitting the alcohol.

In the first two-thirds of the cases the patients had a thorough antiseptic preparation in the wards, the afternoon preceding operation, a preliminary dressing being applied to the field of operation at this time. In the last third, the patients, when not too feeble, received a thorough tub bath in the ward on the morning of operation, were then clad in clean linen and placed in a clean bed. The field of operation was commonly shaved the day preceding operation. After reaching the operating room the field of operation was scrubbed with soap and water. In the later cases no scrub brush was used except in hand and foot cases. Ether and alcohol were used, and lastly a solution of 1 : 3000 bichloride of mercury was poured over the operative field. No mask was used over the face of either operator or assistant, but care was taken to talk as little as possible with the face directed toward the wound.

The dressings were sterilized once for thirty minutes under fifteen pounds of pressure, being wrapped in cotton cloth, before being placed in the sterilizer. This outer cloth cover was removed when the dressings were placed on the operating table. The efficiency of the sterilization was tested by control sterilization of septic dressings, sterilized under the same conditions as the surgical dressings.

The catgut employed was prepared by several different commercial houses, each strand being in a separate glass tube.

In a series of cultures conducted with specimens of chromicized gut secured from numerous different manufacturing houses, the cultures were negative. Control cultures were also conducted with this series of observations.

The development of pus so largely in cases in which buried chromicized gut sutures were used, its late appearance, the fact that it was almost always at the site of the knot, and the further fact that cultures from this pus on examination usually proved to be sterile, and also that suppuration ceased with the evacuation of the knot, all these facts together strongly suggest that the large knot acted as a foreign body, and being near the surface, induced secondary infection.

The conclusions reached after a bacteriological study of the hands of operator and assistants is that washing the hands in soap and water, bathing them in a solution of bichloride of mercury, 1 : 5000, and encasing them in rubber gloves boiled and filled with the same solution of bichloride of mercury is a thoroughly reliable method.

The clinical results obtained seem to show that a general bath and clean linen are as efficient as to attempt sterilization of the field of operation in the ward. The field of operation may be prepared with entire safety upon the operating table. The face mask does not appear to be an essential to aseptic operations. The rubber glove, if properly made, is no impediment to the operator accustomed to its use. It is an almost absolute protection to the patient from the hands of the operator. Only second in importance to its value to the patient is its value to the operator in protecting his hands from infection. While the writer suffered not infrequently from slight infections from hangnails or pricks by needles made during operations, previous to the use of gloves, he has not had a single infection of the hands of any sort whatever in the long series of operations in which gloves have been used. Compared with these great advantages to both patient and operator the cost of rubber gloves is of small consideration. The form and quality of the glove is of much importance. The writer's observation of the gloves manufactured in Europe has been that they are usually of unsatisfactory form and quality.

Since No. 3 chromicized catgut was employed in so large a proportion of cases in which pus developed after operation, and since the pus did not appear, as a rule, until many days after operation, and then occurred at the site of the knot, and the further fact that the suppuration commonly ceased with the evacuation of the knot of gut, it would seem that the chromicized gut leaves something to be desired as a suture material, especially when employed near the surface of a wound. Doubtless a small-sized chromicized gut is less liable to cause difficulty than a large size.

In conclusion we would present the above methods as at once simple, economical, time-saving, of easy application under a wide range of conditions, and thoroughly reliable.

The simple conditions are to wash the hands and arms thoroughly, taking care not to injure the skin with the scrub brush or the matrices of the nails with the nail cleaner, and after washing them thoroughly in a solution of bichloride of mercury to encase the hands while operating in rubber gloves filled with the same solution.

SERIES A.—Harrington's Solution.* Gloves in sterile water

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner	0.15	Clean	4	Negative.
	0.60	Clean	2	"
	0.30	Septic	2	"
	0.15	Clean	2	"
	0.40	Septic	2	"
	0.30	Clean	2	"
	0.30	Clean	2	"
	0.50	Clean	2	"
	0.30	Septic	2	"
	0.50	Septic	2	"
	0.60	Clean	2	"
	0.20	Clean	2	"
		Total . .	26	

SERIES B.—Harrington's Solution, without HCl.* Gloves in sterile water.

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner	0.30	Clean	6	Negative.
	0.35	Clean	4	"
	0.60	Septic	4	"
	1.30	Clean	4	"
	0.20	Septic	2	"
	0.15	Septic	4	"
		Total	24	

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* Harrington's Solution:

Alcohol, 95 %	640 c.c.
Hydrochlorc acid . . .	60 c.c.
Water	300 c.c.
Bichloride of mercury	0.8 gm.

SERIES C.—Gloves in sterile water.

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner Alcohol, 70 %	0.40	Septic	2	Negative.
	0.30	Clean	4	"
	0.50	Septic	[illegible]	"
	1.20	Clean	2	"
	0.45	Clean	2	S. pyogenes albus.
	0.50	Clean	4	" "
	0.15	Septic	2	Negative.
	0.60	Septic	5	"
	0.60	Septic	1	S pyogenes albus.
	1.20	Clean	2	" "
	0.40	Septic	2	" "
	0.60	Clean	2	Negative.
	0.35	Septic	2	S. pyogenes albus.
	1.30	Clean	3	" "
	1.30	Clean	1	Negative.
	0.20	Clean	2	"
	1.10	Clean	4	S. pyogenes albus.
		Total .	42	

SERIES D.—Gloves in bichloride solution, 1 : 5000.

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner Alcohol, 70 %	0.60	Clean	6	Negative.
	1.30	Clean	6	"
	0.60	Septic	6	"
	1.20	Clean	6	"
	0.20	Septic	2	"
	0.35	Clean	10	"
	0.30	Clean	15	"
	0.10	Septic	4	"
	0.15	Septic	2	"
	0.50	Clean	6	"
	0.30	Clean	1	S. pyogenes albus.
		Total .	64	

SERIES E.—Gloves in bichloride solution, 1 : 5000.

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner	1.15	Septic	[illegible]	Negative.
	1.15	Clean	12	"
	1.30	Septic	10	"
	0.45	Clean	13	"
	1.45	Clean	2	"
	0.20	Clean	6	"
	0.50	Septic	12	"
	0.60	Clean	8	"
	0.40	Septic	6	"
	0.40	Clean	4	"
	0.30	Clean	16	"
	2.00	Clean	6	"
	0.15	Clean	4	"
	0.45	Clean	1	Hay bacillus.
		Total .	102	

SERIES F.—Gloves in bichloride solution, 1 : 3000.

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner Alcohol, 70 %	0.60	Septic	6	Negative.
	0.45	Clean	4	"
	0.50	Clean	8	"
	0.50	Clean	1	S. pyogenes albus.
	0.15	Septic	4	Negative.
	0.30	Clean	8	"
	0.40	Septic	8	"
	1.20	Clean	4	"
	0.60	Clean	10	"
	1.45	Clean	6	"
	0.15	Clean	4	"
	0.30	Septic	12	"
		Total . .	75	

SERIES G.—Gloves in bichloride solution, 1 : 4000.

	Time.	Nature.	Number.	Result.
WASHING. Soap, water Scrub brush Nail cleaner Alcohol, 70 %	0.40	Septic	6	Negative.
	0.30	Clean	10	"
	0.50	Septic	10	"
	1.40	Clean	2	"
	0.15	Septic	6	"
	0.60	Clean	2	"
	1.20	Clean	8	"
		Total .	44	

HERNIAS.

No.	Diagnosis.	Operation.	Suture material.	No. of days after operation.	Cultures when taken.	Nature of infection.	Result.
1962	Hernia, inguinal	Herniotomy	Chromic gut	7	....	Stitch abscess	Recovery.
3054	“	“	“	10	....	“	“
3105	“	“	“	11	....	“	“
3225	“	“	“	5	....	“	“
3836	“	“	“	12	....	“	“
4646	Hernia, femoral	“	“	13	....	“	“
4657	Hernia, inguinal	“	“	8	....	“	“
5013	“	“	“	13	....	“	“
5214	“	“	“	12	....	“	“
5742	“	“	“	7	....	“	“
5749	Hernia, double	“	“	10	....	“ (one side)	“ “
1206	Hernia, inguinal	“	Silk	10	Staph. pyog. aureus	“ “	“ “
1257	“	“	Silver wire	21	“	“	
1313	“	“	Kangaroo tendon	7	“	“	“
3054	“	“	Chromic gut	10	....	“	“
3105	Hernia, strangulated	(cocaine anæsthesia)	“	11	....	“	“
3225	Hernia, inguinal	Herniotomy	“	4	....	“	“
3445	“	“	“	11	....	“	“
3836	“	“	“	12	....	“	“

APPENDICITIS.

No.	Diagnosis.	Operation.	Suture material.	No. of days after operation.	Cultures when taken.	Nature of infection.	Result.
1472	Appendicitis, chronic	Appendectomy	Not stated	10	....	Stitch abscess	Recovery.
1475	“	“	“	8	....	“	“
3043	“	“	Chromic gut	10	....	“	“
3602	“	“	“	12	....	“	“
1352	Appendicitis, acute	“	Not stated	10	Staph. pyog. aureus.	“	“
1668	Appendicitis, chronic	“	Chromic gut	4	....	“	“
1883	“	“	Not stated	2	....	Pus in wound	Died 6th d. pneumonia.
3043	“	“	Chromic gut	9	....	Stitch abscess	Recovery.
3319	“	“	“	2	....	“	“

MISCELLANEOUS LAPAROTOMIES.

No.	Diagnosis.	Operation.	Suture material.	No. of days after operation.	Cultures when taken.	Nature of infection.	Result.
1435	Hernia, ventral	Laparotomy	Chromic gut	10	....	Stitch abscess	Recovery.
2069	Salpingitis	Salpingo-oöphorec'my	“	9	....	“	“
2458	Hernia, ventral	Laparotomy	“	5	....	“	“
4464	“	“	“	12	....	“	“
1242	Salpingitis	Salpingo-oöphorec'my	Silkworm gut	7	Staph. pyog. aureus.	“	“
1255	Dilated stomach	Gastroenterostomy	“	...	....	Peritonitis.	Died 5th day
1380	Carcinoma stomach	“	“	10	....	Stitch abscess	Recovery.
2019	Tubercular salpingitis	Salpingo-oöphorec'my	Chromic gut	27	....	“	“
2177	Cystic ovaries	Oöphorec'my	Not stated	7	....	“	“
4984	Uterine fibroid	Hysterect'my abd.	Chromic gut	1	....	“	“

VARICOCELE.

No.	Diagnosis.	Operation.	Suture material.	No. of days after operation.	Cultures when taken.	Nature of infection.	Result.
2481	Varicocele	Excision	1 silkworm gut stitch	6	....	Stitch abscess	Recovery.
3947	"	"	Chromic gut	8	....	"	"
2953	"	"	"	7	....	"	"
3022	"	"	"	21	....	"	"
3227	"	"	"	5	....	"	"
3729	"	"	"	11	....	"	"
3947	"	"	"	8	....	"	"
4006	"	"	"	7	....	"	"

VARICOSE VEINS.

1930	Varix leg	Circular division	Not stated	10	....	Stitch abscess	Recovery.
4555	"	Phlebectomy	"	6	....	"	"
1299	"	"	Plain catgut	4	Staph. pyog. albus	"	"
1390	"	Circular division	Not stated	4	....	"	"
1498	"	Phlebectomy	Silkworm gut	9	....	"	"
2753	"	"	Not stated	4	B. mucosus capsulatus	"	"
3302	"	"	Celluloid thread	10	....	"	"

MISCELLANEOUS.

1732	Hydrocele	Excision	Not stated	4	....	Stitch abscess	Recovery.
4069	Bursa olecranon	"	"	6	....	Erysipelas	"
4527	Movable kidney	Fixation	Chromic gut	12	....	Perinephritic ab	"
1485	Carcinoma mammæ	Excision	Silk suture	11	....	Stitch abscess	"
1906	Deformed toe	Amputation	Silkworm gut	5	....	"	"

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SUPERNUMERARY THYROID AT BASE OF TONGUE

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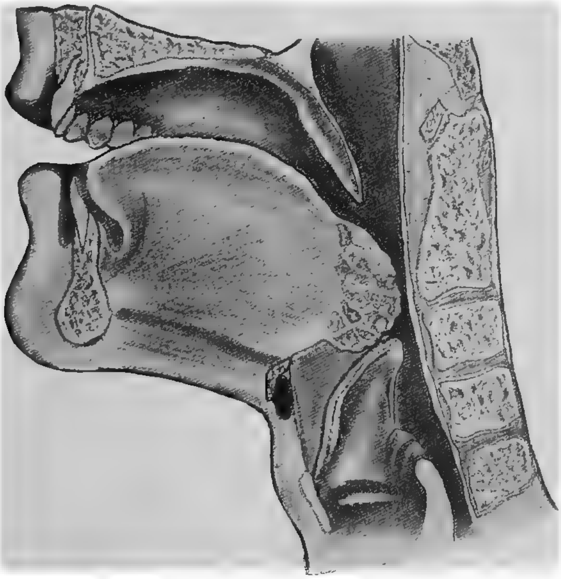
Benign tumors of the tongue are of so rare occurrence, that the following case seems worth reporting.

K. B. Female. Aet. eighteen years, entered Lakeside Hospital Oct. 26, 1903. Her family and personal history were negative. She was anæmic and delicate in appearance. Three years before a physician had examined her throat on account of a complaint of chronic catarrh. He then noticed an enlargement on the dorsum of the tongue.



Accessory thyroid gland upon dorsal surface of tongue.
Drawing by J. M. Ingersoll.

On admission to the hospital the following history was obtained. The patient complained of difficulty in speaking, which had been gradually increasing for three years. During the past four months there had been some difficulty in swallowing, and on exertion respiration was impeded.

Examination by Dr. Ingersoll was as follows: The nose and naso-pharynx were normal. The base of the tongue was covered by a hemispherical shaped tumor, about four centimeters in diameter, projecting backward from the base of the tongue until it touched the posterior pharyngeal wall. The covering of the tumor appeared to be the normal tissue at the base of the tongue and was not inflamed. The epiglottis and the larynx were completely hidden by the tumor, which was firm and moved only with the tongue. There was no pain referable to it and no glandular enlargement.

Operation by Dr. Allen. The growth was removed Oct. 28, 1903. Chloroform anæsthesia was employed and the patient was placed in the dorsal position with hanging head. It was decided to enucleate the tumor if possible without any external incision or division of bone, in order to avoid disfigurement. The tongue was seized with forceps and drawn as far forward as possible. The fingers of the operator could then be hooked behind the tumor, drawing it forcibly forward, so as to bring it nearly to the line of the teeth. A small incision was made at the base of the tumor, along its anterior margin. This caused very slight hemorrhage. The fingers were then carried through the incision, below the tumor, separating it from its bed in the dorsum of the tongue. Since no appreciable hemorrhage occurred it was thought the lateral attachments might safely be separated. This separation was begun upon the left side. On cutting through the mucous capsule on this side there was a very profuse flow of blood, so copious as to threaten asphyxiation on the one hand, and a fatal hemorrhage on the other. The necessity for haste left no other possibility than instantly to divide the remaining attachments and pack the cavity with gauze. While this decreased the flow of blood it by no means controlled it. Since the tissues on the left side of the tongue had been divided by a clean cut of the scissors, it was thought that ligature of the lingual artery on this side might control the hemorrhage. Accordingly, the artery was quickly ligated through an external incision, the pressure of gauze in the wound being continued. By these combined means hemorrhage was controlled. The patient was thoroughly exsanguinated and in collapse.

An intravenous infusion of 500 c.c. normal salt solution was given at once, and 1,000 c.c. were given about three hours later.

About two hours after the operation the patient's breathing was so embarrassed, doubtless due to the large amount of gauze packing, that it was necessary to perform a tracheotomy. With the removal of the gauze packing, two days after the operation, the patient improved rapidly and was dismissed from the hospital cured, all wounds healed, about two weeks after the operation.

The operation is reported thus at length to show the dangers incident to hemorrhage in the operation and the necessity of adopting means to avoid it. This might be accomplished by the application of clamps to the sides of the tumor before the lateral attachments of the tumor were divided. Doubtless ligature of the lingual arteries would be of assistance. Division of the jaw in the median line and separation of the tongue from the horizontal ramus by means of an external opening below the jaw and at the side would give better access to the tumor and enable the operator to control hemorrhage. All these means have, however, the disadvantage of causing disfigurement. Although the operation was successful the hemorrhage attending it was alarming.

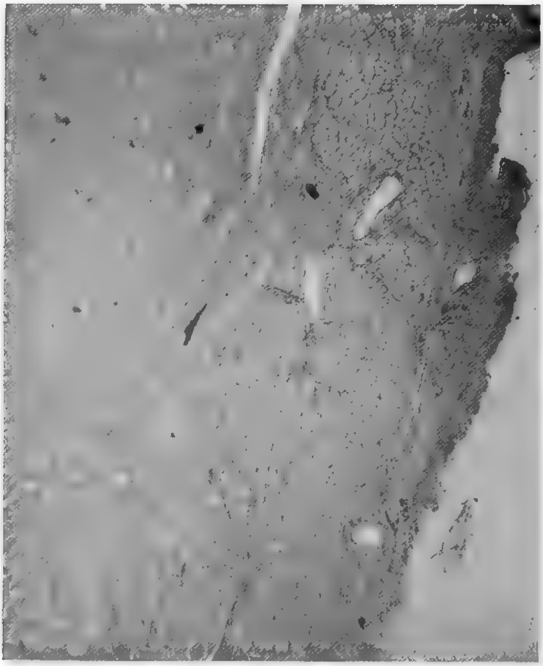
Pathological Report, by Dr. Ludlow.

Gross Description. The mass from the base of the tongue is four centimeters in greatest diameter, and resembles an egg in shape, with its long axis antero-posterior. It is somewhat flattened on its lower surface and the inferior portion is somewhat more blunt than the superior. The dorsal surface of the tumor shows mucous covering which presents numerous fine folds. Blood vessels are very numerous beneath this mucous membrane. Some of the muscular tissue of the tongue was removed with the tumor.

On section the tumor seemed to be distinctly encapsulated and divided into three very distinct lobes by trabeculæ of connective tissue. The inferior lobe is largest, and contains a cavity one-half cm. in diameter, filled with a dark bloody fluid. A smaller cavity is found in the middle lobe and a still smaller one in the superior lobe. The cut surface presents a yellowish-white appearance and shows numerous red areas the size of a pin's head. The tumor as a whole is rather soft and cuts easily. It resembles glandular tissue. A lymph gland removed from the incision made in ligating the left lingual artery is rather firm and normal in appearance.

Sections were taken from the tumor mass through the mucosa and underlying tissue and from different portions of the tumor. Both the celloidin and paraffine methods were used.

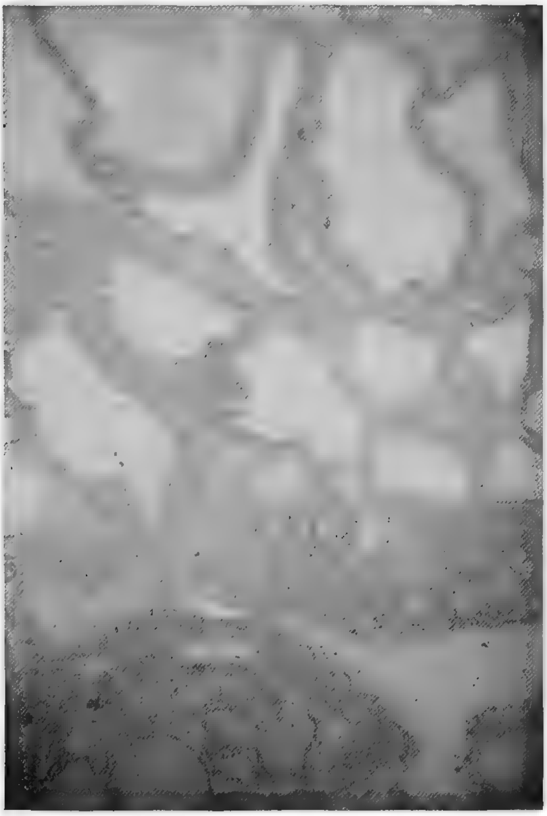
Section A. Through mucous membrane and tumor, showing only small portion of tumor. The surface of the section is covered by squamous epithelium, presents a wavy line which in some places is projected into distinct papillæ. The outer layers of ephithelium are much flattened and stain a deep pink, while toward the base the cells are more ovoid in shape and take a blue stain. The papillæ are filiform in character. The tunica propria and sub-mucosa consist of connective tissue and numerous elastic fibers which form the support for large numbers of glands. These glands are of the branched tubular type The walls of the tubules consist of a structureless membrana propria and gland cells; the latter are broad columnar elements, possessing a firm cell membrane and showing on deep blue staining small oval nuclei, pressed flat against the cell wall, thus presenting a picture of mucous glands loaded with secretion. In addition to the connective tissue, many bands of muscular fibers are found disposed in different planes, and thus appear in cross, longitudinal, and oblique section. The muscle is striated and the fibers interlace. The veins and arterioles show marked congestion. The tumor lying beneath the muscle fibers is surrounded by a dense fibrous capsule which sends down large trabeculæ from which a smaller net-work of connective tissue spreads throughout the remainder of the section. This framework forms support for a large number of gland tubules and in many places shows a hæmorrhagic infiltration. The tubules differ greatly in diameter and are lined by a simple layer of



SECTION A

cubical epithelial cells. The nuclei are oval in shape, stain a deep blue and are situated near the center of the cell. The tubules appear in cross and oblique section; the latter being cut on the tangent, show the tubules apparently filled with epithelium. The contents of many of the tubules consists of a deep pink staining, homogeneous material, colloid substance, which is also found in the lymph spaces. Other tubules are filled with red blood cells.

The blood vessels are very numerous and break up into capillaries that form a net-work about the tubules. This structure corresponds in every particular with that of the thyroid gland.



Section B

Section B. This section was taken through a deep portion of the tumor. The main portion of the section presents an appearance similar to that described in Section A. In one portion of the section the tubules are greatly dilated and filled with colloid material, but otherwise the section presents nothing additional to the above.

A lymph gland taken from the incision below the jaw on the left side is normal in appearance.

Supernumerary thyroid and gland tissue may occur in different portions of the body. One of the favorite positions is at the base of the tongue in the region of the foramen cæcum. The researches of His, made on very young human embryos, have enabled the tract extending from the foramen cæcum to the pyramidal lobe of the thyroid gland to be fully traced. This has proved of great service in explaining the occurrence of cysts and tumors in this region.

Hickman in 1868-9 described a congenitial tumor of the tongue extending from the circumvallate papillæ nearly to the epiglottis, and deeply into the tongue which caused death by suffocation sixteen hours after birth. The tumor was described at that time as consisting of hypertrophy of racemose glandular structures with connective tissue and blood vessels.

Bernays, in October, 1888, St. Louis Medical and Surgical Journal, reported a case of a supernumerary thyroid situated at the base of the tongue. In April of the following year, R. Wolf of Hamburg, reported a similar case.

In 1890 Butlin described two cases of tumors in the portion of the foramen cæcum, and gave drawings of the miscroscopic sections. They would formerly have been described as adenomata; but in accordance with the opinion expressed by Bernays and Bland Sutton, they were later thought to consist of thyroid gland tissue.

Winslow, of Baltimore, American Medicine, Dec. 13, 1902, records thirty cases of accessory thyroids and in addition reports a case occurring in his own service. The case reported in this article presents a striking similarity to Winslow's case, both in the clinical history and pathological findings.[1]

On Jan. 7, 1905, a letter received from the patient whose case is reported above states that her throat causes her no trouble. She states, however, that the left side of her tongue seems slightly paralyzed.

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[1] For a bibliography the reader is referred to Winslow's excellent article above mentioned.

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TRAUMATIC DEFECTS OF THE SKULL. THEIR RELATION TO EPILEPSY. A CLINICAL AND EXPERIMENTAL STUDY OF THEIR REPAIR.*

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THE *Saturday Evening Post* recently said, "The main trouble with the man who announces a new theology is that he forgets his quotation marks." In a similar manner the medical man who thinks he has fallen upon a new idea usually finds he has been anticipated by some one wiser than himself. Often he finds his idea is not only old but valueless.

After spending considerable labor in elaborating a method for repairing skull defects, the writer finds that in certain details he has been anticipated by the publication of the Koenig-Müller method of bone grafting. The first operation by the writer, after the method to be described, was performed in Lakeside Hospital, Aug. 22, 1900.

Before discussing the question of the repair of defects of the skull, it may be well to consider the conditions making such repair desirable. These conditions relate chiefly to epilepsy, the result of traumatism. They should include also periodical attacks of dizziness, headache, numbness, palpitation of the heart, etc.

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*Read at a meeting of the Boston Medical Library, Dec. 6, 1905.

To determine accurately the relation borne by traumatism to the production of epilepsy is by no means easy. Many grave injuries to the skull are not followed by epilepsy or ill effects of any kind. Sometimes manifestations of the sort are so long delayed that it is difficult to show that there is any relationship between them. Doubtless there are many cases of epilepsy following trauma in which the trauma has been forgotten.

That epilepsy may, and often does result from trauma, seems to be a universal belief. As bearing upon this belief the statistics of injuries to the head during our Civil War are of interest. Of 167 skull injuries, 23 or 13.7% are on the pension list as suffering from epilepsy. In the Franco-Prussian war there were 571 cases of recovery from gunshot wounds of the skull. Of these 25 cases or 4.3% developed epilepsy. If to the cases of epilepsy are added cases suffering from periodical attacks of dizziness, numbness, trembling, etc., the number is raised to 26.7%. The fact that epilepsy of non-traumatic origin usually develops early in life makes it highly probable that in these cases there is a causal relation between the trauma and the epilepsy.

In discussing traumatic epilepsy it must be borne in mind that the symptoms may result, not from injuries to the skull alone, but to the brain as well. They may result also from the formation of new scar tissue as well as from hyperostoses. The stimulus to attacks of epilepsy may also arise from irritation to peripheral nerves.

If the commonly accepted view be correct, *viz.*, that epilepsy often follows skull injuries, the important questions before us as surgeons are five: (1) Can they be relieved by operative interference? (2) At what period should such operations be performed? (3) What class of cases are suited to operation? (4) What are the defects of methods commonly in vogue? (5) What operative procedures are best fitted to give permanent relief?

In discussing the first question, *viz.*, the benefits to be derived from surgical interference, one is met at once by the unreliability of the statistics. The published experience of any one surgeon is too limited to permit of positive conclusions. The collected experience of different surgeons is widely at variance. Dougalls and Walsham formerly reported from 60% to 70% of cures following operation. Graf and Braun, after careful study, accepting as cured only such cases as had remained well for three years after operation, report from 2% to 4% of cures. Kocher[1] in considering this subject credits Bergmann with 20 operations and 6 cures, or, if the three-year limit be insisted upon, with 4 cures or 20%. Discussing the subject further he points out that results vary greatly with the conditions found at operation. In 19 cases of trephining, in statistics collected for Kocher by Schar, in which there were found pressing upon the dura, splinters or corners of bone, abscesses or adhesions, and in which these were removed, there were 68.3% of cures. Still better results were found to exist in cases in which the splinters of bone or scars found pressing into the brain were removed by dividing the dura. In the latter cases cure resulted in 88.8% of the cases. It is to be remembered, however, that Kocher classified under the head of cured (Heilungen) cases showing positive improvement following operation, leaving out of consideration the question of final cure. In choosing the three-year limit as indicating cure, it must be remembered that there may be recurrence of epileptic symptoms after a still longer period of immunity.

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[1] T. Kocher: Ueber einige Bedingungen objektiver Heilung der Epilepsie. Centralblatt für Chirurgie.
Bericht der Deutschen Gesellschaft für Chirurgie, 1899, pp. 40, 41.

Interesting as it would be to pursue still further a consideration of the possibility of curing epilepsy by operation, it would take us too far from the chief question to be considered in this paper, *viz., the prevention of epilepsy by the repair of skull defects.*

The second question is, At what period should operations for the relief of traumatic epilepsy be performed?

The prevailing opinion seems to be that early operation is highly desirable, and this is supported by such men as Championnere, Gerster, Starr, v. Bergmann and many others.

There seems little question that by the continuance of any irritation which induces epileptic seizures, a condition is established which may continue even after the primary cause of the seizures has been removed. Thus, notwithstanding the fact that cures have been reported following operations for epileptic attacks recurring seven, ten and even eleven and seventeen years after injury,[2] still every consideration seems to point to the desirability of early operative interference in traumatic epilepsy, provided the cases seem to be suitable ones for operation.

The third question to be considered is, What class of traumatic cases is suited to operation?

The purpose of this paper is to show that all traumatisms to the skull resulting in bone defects should be repaired as soon as possible, not awaiting the possible development of epilepsy. This phase of the subject will receive consideration later on in the paper. The paper also seeks to show that should epilepsy follow trauma, and the removal of bone be necessary for its relief, the defect caused by operation should at once be repaired.

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[2] Reported by Horsley, Taylor and Schede: Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie, 1899, p. 712.

The fact is not forgotten that many of the gravest skull injuries may never develop epileptic or psychic disturbances. Two children operated upon, one by myself, and one by my late assistant, Dr. Nevison, fell from heights of about fourteen feet upon stone pavements, crushing in the entire vaults of their skulls and causing the most extensive fractures and depressions. In each case, by means of a sharp, curved, steel hook, the bone was lifted into place, the convexity of the cranium was re-established and the children recovered. One case I have followed about eleven years, and no ill effects of any sort have resulted. The second case has been lost sight of.

On the other hand, injuries apparently slight, may cause grave consequences. Unquestionably the cases promising most from operation are those in which the symptoms are the result of pressure upon the brain by spicules or edges of fractured bone, exostoses, scar tissue, etc. If the brain itself be injured, operative procedures promise less. Interesting as it might be to consider the benefits resulting from the removal of portions of the brain cortex as performed by Horsley and others in cases of Jacksonian epilepsy, it would take us too far from the purpose of this paper.

The indications for operation are well stated by von Bergmann.[3]

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[3] Handbuch der practischen Chirurgie. Vol. i, p. 321.

He says, (1) Operation is indicated in recent cases with infrequent attacks.

(2) In cases having manifestations described as Jacksonian epilepsy.

(3) In cases having upon the scalp, or skull evidences of previous injury.

The fourth question is, What are the defects of methods now in vogue?

Nothing will be said concerning the removal of brain cortex or of abscesses or cysts, and it is unnecessary to discuss the methods of removing bone.

For the removal of sections of bone, the exact area of which cannot be previously determined, and when the Omega bone flap does not seem to be indicated, my preference is for the burr drill and the Lane bone forceps. The defective method to which it is desired to call particular attention is that of removing a portion of the skull and leaving the defect unrepaired. Kocher [4] on the other hand, in closing his article on this subject, says, " Often it is not the opening, but rather the closing of the skull which causes harm." He advocates the incision and even the excision of the dura mater, in order to prevent the formation of a new bony covering of the defect, contending that the leaving of a vent (ventil) or even multiple openings tends to equalize intracranial pressure, and thus decreases the tendency to recurring attacks of epilepsy. In addition to his own experience he bases his opinion upon the observations of Schar and Beresowsky of Moscow, to the effect that cases which have remained cured after operation for epilepsy were those in which defects in the bony covering had persisted.

Opposed to this view is the widespread experience that after operation epilepsy and allied conditions are often benefited temporarily, only to recur and be relieved again and again by subsequent operations. The conclusion seems evident that the recurring symptoms are the result of recurring pressure. To discuss this point at length would require more time than is at our disposal.

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[4] Kocher: *Loc cit.*, p. 47.

That epilepsy, the result of trauma, is to be relieved by a permanent skull defect seems wholly improbable. The establishment of the credibility of this view would require more facts than those advanced thus far by Kocher, much as his abilities are respected by every surgeon. In opposition to this view von Bergmann has pointed out the fact that epileptic attacks are often provoked by peripheral irritation, such as neuromata, foreign bodies in the ear, etc., conditions with which defects of the skull can have no connection. It seems probable that removal of pressure and the permanent repair of the skull, restoring its convexity and resistance to external injury, would be far more likely to be followed by permanent benefit.

The fifth consideration is, What operative procedures are best fitted to give permanent relief?

Many methods have been proposed for this purpose, and some of them have been employed for a long time. The method of closing defects in the skull by means of metal plates is one of long standing, but it is not satisfactory. Celluloid plates have also been used for the same purpose, but these also have not met general adoption.

Horsley in his operations for the removal of brain tumors employed the method of re-implanting the disk of bone removed by the trephine.

This method has proved very successful and is applicable in cases where this disk of bone exists. The method does not, however, provide for the covering of old defects where there is no such disk of bone available. Macewen employed fragments of bone removed at the time of operation. These were placed in the defect and served as a scaffolding for the formation of new bone. This method has also proved successful in a certain percentage of cases, but numerous failures are reported.

Another method has been suggested by R. Porges.[5] He reports a case in which as the result of cervical caries an opening in the skull existed 7 cm. long by 5 cm. wide. After incising and reflecting the skull the granulations covering the dura were removed. Over the dura two strips of celluloid were so placed that their extremities were wedged into the diploë, in order to retain them in position. The periosteum with the integument was then laid back over the strips of celluloid and the defect was thus covered and closed firmly.

Grekow[6] of St. Petersburg, has made an extensive series of experiments in repairing defects of the skull. His method is to lay in the defect a thin sheet of thoroughly calcined bone. The bone may be obtained from any source. His observations are based upon a large number of experiments made upon various animals. By this means bone defects may be repaired. He says that bone under these circumstances grows from three sources: first, the diploë; second, the periosteum, and third, the dura. The calcined bone plate serves to prevent adhesions of the dura and periosteum and affords a scaffolding for the growth of new bone, which takes place generally from the periphery. He says that the method is effective in animals and in man, in lesions both old and recent. The process requires three months or more in animals and adult persons. His investigations are extensive and complete and seem to prove the success of his method.

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[5] R. Porges: Centralblatt für Chirurgie, 1903, p. 397.

[6] Grekow: Contribution à l'étude des manques de substance osseuse du crane, St. Petersburg.

Another method is that suggested by Müller,[7] and employed by Koenig, being called the Müller-Koenig method. This method is, after laying bare the skull defect, to form a flap of similar size and outline from the adjoining portion of the skull. The skin and periosteum are left attached to the bone. By means of a cutting chisel the outer table of the bone lying beneath the flap is separated from the inner table and a flap thus created which is made up of integument, periosteum and fragments of bone, is transplanted so as to cover the defect.

Still another method has been suggested by Bunge.[8] This is to form a flap in a similar manner, consisting, however, only of periosteum and fragments of bone similarly obtained. The base of the flap is preserved and the whole is transplanted so as to cover the defect.

At what time the Müller-Koenig method was first employed I have been unable to discover. That of Bunge is first described in 1903. Neither of the latter methods was known to the writer until a short time ago, long after the method to be described was successfully employed.

The method proposed by the writer for covering defects of the skull was first employed Aug. 22, 1900. It is as follows:

The scalp is removed from over the defect in the skull and the connective tissue covering the brain is carefully dissected away. Since the scar tissue and dura are often inseparable, the pia mater covering the brain tissue may thus be exposed over the entire area. In certain cases in which the injury to the brain tissue has occurred as the result of traumatism, it may be necessary to trim away a portion of the brain with the scissors, since the connective tissue may be firmly connected with the brain tissue itself. The borders of the opening are carefully examined to see if any portion of the bone projects downward, and if so it is removed by means of rongeur forceps. Any hemorrhage which occurs is carefully stopped, since it is an essential part of the operation that all hemorrhage should be controlled before the bone flap is inserted. When the surface upon which the bone flap is to be implanted has thus been made clear and hemorrhage has been checked, the scalp is removed from an added area of the skull of equal size with the opening. In doing this care is taken that the periosteum covering the skull be left intact. It is also important that the portion of skull laid bare be as thick as possible. Thus, the posterior parietal region is preferable to the temporal region. Upon the area thus laid bare a circular or elliptical incision is made, blocking out a portion of periosteum equalling in form and size the defect which is to be covered. A sharp, narrow chisel is then employed to split from the outer surface of the skull the portion of bone adherent to the overlying periosteum. To separate this bone from the skull the blows of the chisel should be short and quick so that the portion of bone split away reach no deeper than the diploë. In the removal of this area of bone with attached periosteum, the tendency, of course, is for the bone to be separated into small fragments, and to roll upward and outward. By placing the graft thus obtained between two gauze sponges moistened in warm normal salt solution and laying it upon the table, it may be flattened out by a few slight blows of the mallet. The plate of bone thus prepared is laid upon the opening in the skull, the bone being next to the brain. The wound is then closed by drawing over it the scalp and suturing it loosely in place. A cigarette drain made up of gauze and surrounded by gutta percha pretective tissue is inserted through the incision at the dependent point, so that any excess of blood may be drained away into the dressing. The dressings are changed ordinarily on the second day in order to remove the cigarette drain, after which a second bandage is applied. This bandage remains in place for perhaps six or eight days longer, or until the wound has entirely healed. By this method seven cases have thus far been operated.

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[7] **Koenig: Lehrbuch der Chirurgie, 1903, p. 129.**

[8] **Bunge: Verhandlungen der Deutschen Gesellschaft für Chirurgie, p. 37, Centralblatt für Chirurgie, 1903.**

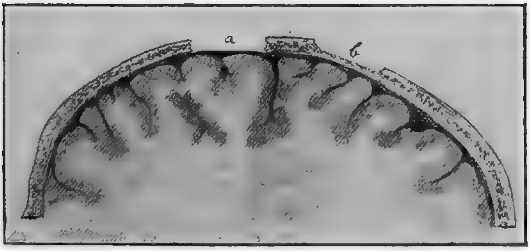

FIG. 1. Section of skull. Diagram showing (a) opening in skull and (b) location from which bone-graft was removed.

CASE I. F. H. Male. Aged, nineteen years. The patient had been injured on the right side of the head in November, 1892. After four and a half years, in July, 1897, he developed symptoms of excitability, which made it necessary to send him to the State Hospital in Newburg. Here his condition of excitement greatly increased. The only hope of relief seemed to lie in the possible benefits of operation, the thought being that by relieving the pressure at the point of injury some benefit might accrue to the patient. He was admitted to Lakeside Hospital in March of 1898. His state of excitement was so great that it became necessary to place a guard over him day and night. At this time a portion of the skull, 4 cm. in diameter, in the right fronto-temporal region was removed. The opening was covered by the scalp and the patient was sent home. His general condition improved very greatly and he remained well for about two years, performing ordinary duties about his home. He

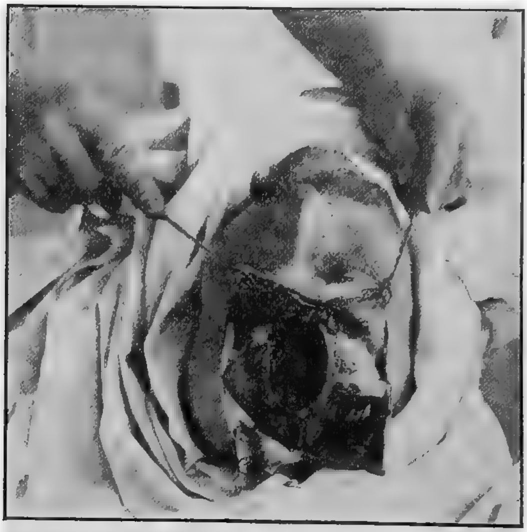

Fig. 2. Skull defect prepared for graft.

came to the hospital again, however, on Aug. 22, 1900, the statement being made that he had recently developed mild excitement, in no way to be compared with that which had previously existed, but such as had made him desire to go to the State Hospital for the Insane at Massillon. In thinking the case over it occurred to me that since the patient had been so greatly relieved for the period of two years following his first operation, this might have resulted from the removal of the pressure upon the brain. Later, as the scar tissue contracted, it could have renewed pressure upon the brain, and thus have caused a return of excitability. In considering how the patient might be relieved, the method of bone grafting which has been described suggested itself. The operation was performed on Aug. 22, 1900, and the patient left the hospital on Oct. 6.

On June 27, 1903, nearly three years after this operation, he returned for re-examination, saying that since the last operation he had been entirely well. He further said that after he returned home the defect in the skull, which on dismissal had been hard, appeared to grow soft, but that after a time it had become hard again. From this report it seems probable that the chips of bone adherent to the dura mater had been absorbed, but that later bone had been reformed. Examination at this time showed that the former defect was covered by solid material through which no pulsation could be felt and that there was no indentation upon firm pressure. The evidences are, therefore, that bone had been formed. The patient remained perfectly well until the 25th of July, 1903, having occupied a responsible position, with entire satisfaction to his employers. The responsibility was, however, large, and it seemed to be too much for him. He confided to a friend that he thought it would be impossible for him to be cured permanently and he deliberately ended his life.

Case II. W. B. Male. Aged, seventeen years. The patient was admitted to Lakeside Hospital, July 10, 1903. The night before admission to the hospital the patient fell from a street car, striking upon his head. He was unconscious from this time until admitted to the hospital, eighteen hours after injury. He was very restless, complained of severe headache and also of pain in the back of his neck. Patient was in good physical condition. On examination of the skull the scalp over the vault of the skull was found to be œdematous, but no depression could be felt. The eyes showed nothing abnormal. The patient

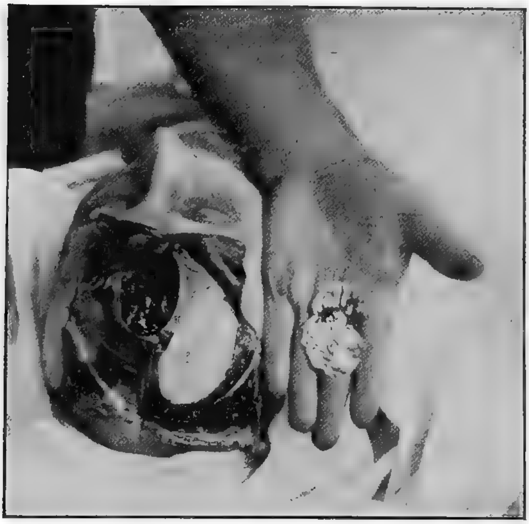

FIG. 3. Graft removed from area covered with white paper and lying bottom upwards in operator's hand.

continued to have severe headache. He was, however, conscious and did not develop paralysis of any sort. The pain, however, was so severe, that it was decided, on July 13, to open the skull. A crucial incision was made over the vault of the skull in the anterior parietal region. On exposure of the skull no distinct fracture could be made out. There was, however, a seeming separation of the longitudinal suture and the sagittal suture. By means of a burr drill and rongeur forceps a portion of the right parietal bone, just to the right of the median line, was removed. The opening was 9 cm. long and 7 cm. wide. Underneath the skull, lying between it and the dura mater, was an area filled with a blood clot, separating the dura from the skull a distance of 1 cm. This was quite adherent to the dura and was removed with some difficulty. No attempt was made at this time to close the defect in the skull itself by bone graft. The reflected integument and periosteum were brought back, united by a few sutures and room was left between the flaps for drainage. The patient made a rapid recovery from this operation and was dismissed from the hospital on Aug. 11, 1903. The large size of the opening made it seem wise to close this later on by a bone graft. Accordingly, the patient was re-admitted to the hospital on Sept. 19, 1903. Since the first operation the patient had suffered much from headache, particularly over the eyes and around the ears. He had done no work. When he tried to read he had pain in the eyes and also increase of pain in the head. He had had, however, no epileptic attacks. On examination of the field of operation a depression could be felt, which became even with the rest of the skull when the patient was lying down. The operation for the closure of the skull was undertaken Sept. 21, 1903. A bone graft, secured in the manner described, was removed from beside the original defect and laid in place. The recovery was uneventful and the patient was discharged on Oct. 31.

The patient was re-examined Nov. 17, 1905. There was an irregular depression to be felt, corresponding to the original defect of the skull. The defect was about 8 mm. in depth, representing approximately the thickness of the skull at this point. On firm pressure there was no yielding of the surface and no pulsation was to be felt. The defect appeared to be repaired by the formation of new bone. The patient had been entirely relieved from headache and was perfectly well in every respect since the time of the second operation.

Case III. W. J. C. Male. Aged, thirty-five years. Single. The patient was admitted to Lakeside Hospital, July 30, 1903. Previous history negative. In September, 1894, he was struck by a locomotive, and in falling hit his head upon a piece of iron. He was not conscious of his surroundings for about two weeks. During this time he was in the West Penn Hospital at Pittsburg, Pa. He says that the doctors

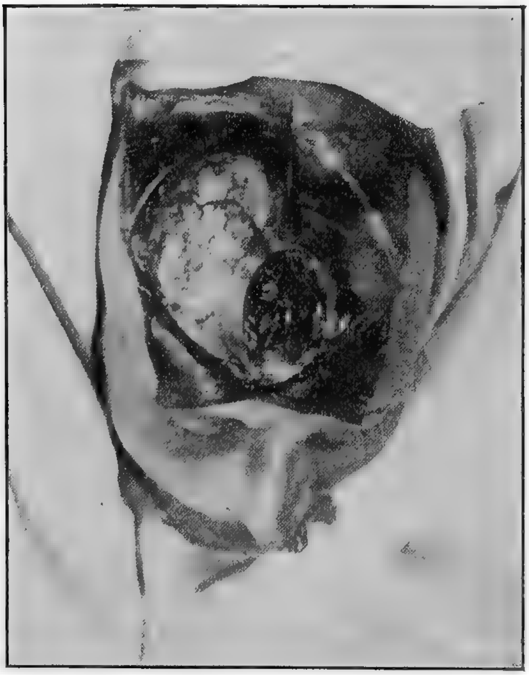

Fig. 4. Graft laid in position filling defect. Piece of paper shown in Fig. 3 removed to demonstrate appearance of skull after upper table (graft) has been taken off.

considered his condition hopeless, and did not operate in any way. He was in the hospital for three months. There were no paralyses of any kind. Seven months after injury he had his first epileptic attack. These attacks recurred at intervals of about a month until August of the same year, when his skull was operated upon by Dr. Buchanan of the West Penn Hospital. After this time his fits came back at intervals of about two months. A year later he was referred by Dr. Buchanan to Dr. Keen of Philadelphia, who declined to operate. On Feb. 22, 1897, he was operated upon by Dr. McGrew of the Allegheny General Hospital. After this he improved so that he had only six epileptic attacks in the next six years. The last one was in March, 1903. On admission to Lakeside Hospital he was found to have an opening in the skull 5½ cm. wide by 6 cm. long. This opening was 2 cm. to the right of the median line and in the parietal bone above the right auditory meatus.

Operation was performed July 31. Crucial incision. On exposing the defect in the skull it was found to be filled with a thick layer of fibrous tissue. Embedded in this tissue was found a piece of gold foil which had been inserted at the last operation to prevent the adhesion of the scalp to the dura mater. The cicatricial tissue was found adherent to the dura through a portion of the wound. A bone flap, the size of the opening, was secured toward the median line and placed in the defect. This was then covered with a skin flap which was sutured in place except for a small opening for a cigarette drain. On Aug. 17, the patient had an epileptic attack lasting for about one minute. No further convulsions occurred and the patient was dismissed from the hospital on Oct. 26, 1903.

In January, 1905, the patient was re-examined. Excepting for one very small point where the surface yielded very slightly on firm pressure, the entire defect seemed to be filled with new bone. The patient was persuaded to permit an incision to be made in the scalp in order to determine whether new bone had been formed. This was done under cocaine. The knife came down upon a firm tissue which had every appearance of bone, being hard so that it could not be cut with the knife, and having a white and glistening appearance. It seems that there can be no question that the tissue thus found was bone. Since the last operation the patient has had two attacks of epilepsy, one Feb. 19, 1904, and another July 20, 1905. Aside from this he has been perfectly well and able to work. He was last examined March, 1906.

Case IV. G. N. Male. Aged, twenty-eight years. Single. Admitted to hospital Oct. 10, 1903.

The patient was well until seven years before admission to hospital. At that time he fell under a horse's feet, and the horse's shoe penetrated his forehead. He was told " there were cracks in other portions of the skull." There were no immediate symptoms. Two weeks after the injury two ounces of pus were evacuated. Details of this operation were not given. This operation was followed by apparent recovery.

On Sept. 30, 1903, while talking with a friend on the street, patient says he experienced a peculiar creeping sensation, as of a rush of blood to the head. This was accompanied by pain in the right parietal region and a sensation of intense weakness. He remembers being placed in a carriage and taken home, but nothing more. On Oct. 2 he had a similar attack. He thinks he did not lose consciousness, but felt very weak after the attack and slept for some time. His physician, Dr. Ashmun, says that the attacks began with rolling of the eyes toward the left side, drawing of the left side of the face to the left and drawing of the whole head to the left. On examination a stellate scar was found in the forehead above the right eye. At the center of this was a slight depression corresponding to the loss of bone following the previous operation. The opening was said to have been originally about the size of a dollar, but its diameter had been decreased. The site of the old injury was laid bare by a semi-circular flap. The connective tissue was removed from the site of the old injury and the edges of the bone were refreshened with the rongeur forceps. The surface of the brain was found to be infiltrated with connective tissue at the site of the former abscess, so that normal brain tissue was not seen. A bone flap was then secured above and to the outer side of the opening, and the wound was closed with suture except for a cigarette drain. On Oct. 14, the patient had a convulsion at 7 A.M., followed by six others during the day. His attacks resembled those occurring before operation. After that time patient had no recurrences of epileptic seizures. The recovery was uneventful and the patient left the hospital on Oct. 31. Examination at this time of the point of operation showed that there was considerable resistance to pressure and that there was no pulsation. Patient was examined March 21, 1906. He is in business and has been perfectly well since the time of his operation.

CASE V. H. C. Male. Aged, thirty-two years. Admitted to the hospital Nov. 21, 1904.

Patient had been in good health until fifteen months before admission to the hospital when he was kicked by a horse in the right temporal region. He was rendered unconscious and the skull was fractured. At this time an operation was performed and three pieces of skull were said to have been removed. The wound healed promptly. Four months after his injury he had his first convulsion. At first these recurred at intervals of about two months. The intervals then became shorter until it was but two weeks, but of late the time between the convulsions has been somewhat increased. The attacks came on with dizziness and a feeling of numbness over the entire body. He thinks that he also turned his head to one side as the attacks came on, but does not know which side. He remained unconscious for about twenty minutes and was light headed for two hours afterward. Patient is a well-developed man. There is a defect of bone in the right temporal region. It is about 4 cm. long and 1½ cm. wide. Operation was performed Nov. 26, 1904. The defect was laid bare by an incision through the scalp and periosteum. The edges of the bone were found to be markedly depressed and were removed with forceps. No scar was found in the dura mater. The original incision was then enlarged, a bone flap was secured above the site of injury and placed in the wound. On Nov. 27, the patient had a convulsion at about 5 P.M. during which he was unconscious for fourteen and one-half minutes. This recurred at 9 P.M. From this time on the patient's progress was rapid, there were no more convulsions and he was dismissed with a firm cicatrix on Dec. 16, 1904. The defect was resistant to pressure and showed no pulsation.

A letter received from the patient Nov. 16, 1905, says that on July 23, of this year, he had an epileptic attack, the only one since his operation. Since that time he has not felt as well, being light headed.

CASE VI. F. D. Male. Aged, eleven years. Admitted to the hosptial Dec. 5, 1904.

The patient was a well, strong child. When two and a half years old he was struck upon the head by a six-pound quoit pitched a distance of thirty feet. The child was unconscious for five or six minutes. There was a wound in the head which bled freely, but the mother repaired it by the use of plaster. No physician saw the case. About four or five months after this injury the child had a convulsion, These convulsions recurred every four or five months and bore the characteristics of epileptic attacks. The child had his last epileptic attack four or five months before admission to the hospital, and after that his mother says that he was "crazy" for three days. Patient has also had "fainting attacks," and when seized with these he falls down, the attacks lasting but a few minutes, and after these the boy complains of not being able to talk easily. The mother says sometimes he stutters after these attacks. His last "fainting attack" was the latter part of November, 1904. The boy is high tempered but not malicious.

On examination of the patient's skull a small scar about 2 cm. in length was discovered at about the junction of the occiput with the right parietal bone. Nothing further could be felt. The operation was performed on Dec. 9, 1904. A horseshoe-shaped incision, 7 cm. in diameter was made in the scalp.

By means of a burr drill and chisel a piece of bone, 3½ cm. long and 1½ cm. wide, was removed. Although there was a slight depression in the outer table, no depression was found upon the inner table. The dura mater was incised but nothing abnormal could be seen upon the surface of the brain convolutions. A bone flap was chiseled from the skull behind the opening made by operation and the wound was closed except for a cigarette drain. The boy's recovery was uneventful until Dec. 17, and he was up and about the ward. On this day he was noticed to be breathing rather loudly and deeply. On examination it was found that he was unconscious, that his eyes were widely open and slightly rotated to the left. Corneal reflex was present. The boy could not answer when spoken to. He had no convulsion and his muscles were not rigid. There was a hypersecretion of saliva. He remained in this condition for about thirty minutes when he gradually regained consciousness. His convalescence was otherwise uneventful and he was dismissed from the hospital on Dec. 29, 1904.

The patient was re-examined on Nov. 17, 1905. At that time the defect in the skull was found to be firm, not yielding on pressure and showing no pulsation. The surface was slightly irregular. Before operation his parents say the boy was dull and unable to study. At the present time he goes to school and his family report that he is bright in his studies and is perfectly well.

Case VII. F. L. Female. Aged, twenty years. Married.

When a year old patient fell on a rusty iron, striking left side of forehead, driving nail into her head. After this she says she had meningitis for about six months. From that time she was well until sixteen years of age, when she began to have convulsions. In the convulsions she falls to the ground, bites her tongue and has foaming of the mouth. Her first convulsion came with the first menstrual period. She entered the hospital Sept. 10, 1905, and was operated upon for abscess of the breast. During her sojourn in the hospital she had repeated epileptic attacks. Patient had a small scar over the left frontal bone and on palpation the external surface of the bone was found to be somewhat irregular. On Sept. 21 a button of bone, 2 cm. in diameter, was removed with a trephine. Its inner surface was found to be somewhat irregular. The bone at the point of injury was thinner than normal, and there was no pressure upon the dura mater. On examination of the dura there seemed to be a marked increase of connective tissue. Before opening the dura and also afterward there was an escape of a considerable amount of clear fluid. The brain tissue was not normal, but showed an increase of connective tissue. None of the brain tissue was removed. A bone flap the size of the opening

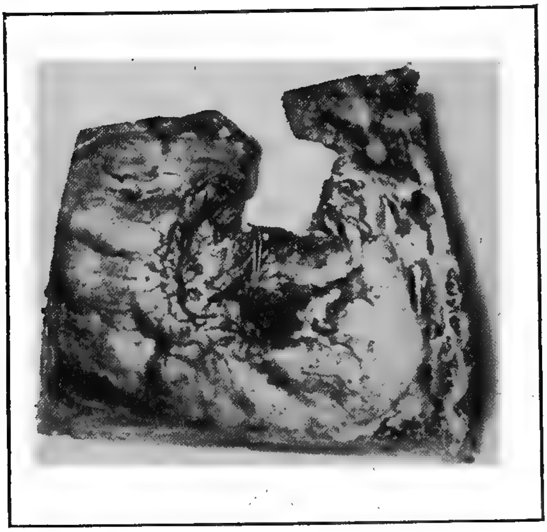

FIG. 5. Skull of dog. Internal surface showing bone graft two weeks after insertion. Rectangular defect made by removing bone for microscopic examination.

was secured just above the trephined bone and used to cover the defect in the skull.

There was a respite in the epileptic attacks immediately following operation, but they recurred at the next menstrual period, and recurred several times again before her dismissal from the hospital on Nov. 5, 1905. The wound in the skull healed by first intention. A cigarette drain was left in place for two days. At the time of leaving the hospital firm pressure seemed to show that the opening was firmly healed.

The seven cases just reported would seem to demonstrate beyond question that defects of the skull can be repaired by the method which has been suggested. In every case operated upon, the wound has healed by first intention and the defect has been repaired by what seemed to be bony structure. The defects are firm on strong pressure, showing no pulsation, and in one case in which a secondary incision was permitted the incision came upon what bore every appearance of being bone.

In order to study more fully the process of repair, a series of observations were undertaken upon dogs. These were carried on by my former assistant and present associate, Dr. Henry L. Sanford, to whom I am greatly indebted. The following is his account of his investigations.

In endeavoring to carry out bone grafting on the skulls of dogs, several obstacles were encountered. The same precautions for securing asepsis were taken that would be employed with human beings, but still it was found difficult to secure and maintain an aseptic field for operation, and it was also hard to devise a dressing which the dogs could not succeed in pulling off. Crinoline bandages put on wet and extending down well on to the nose and back over the neck gave the best results. When dry the dressing hardened into a cast in which the dog seemed very comfortable.

The extremely irregular topography of a dog's skull also reduced the available operating area to the temporal fossæ on each side of the median ridge. Here was found a fairly level space, large enough to yield a graft, and here, too, the formation of the dog's skull most nearly approximates the diploë of the human skull. Medium sized, short-haired dogs with broad skulls were found best adapted for the experiments.

The technique of the operation consisted in turning back from the median line the skin and temporal muscle in a horseshoe flap, taking care not to injure the periosteum. As large an area as the curving contour of the skull admitted was then marked out and chiseled off, so that the graft amounted to a sheet of periosteum, to the under side of which was adherent a layer of bone chips. It was at first attempted to transfer such a graft from one side of the skull to a previously prepared defect of corresponding size in the opposite temporal fossa, but the dogs stood the shock of what was practically a double operation poorly, owing to the enormous bleeding from a particularly large intra-osseous vessel which was met with in every case, and which was necessarily opened in getting off the graft in this only available location.

It was thought that the requirements of the experiment would be fulfilled if, after freeing the graft, the skull defect should be completed rapidly down to the dura in the place from which the graft had been taken and the graft then laid into practically its original position under the new conditions. This proved very successful.

Quite a number of dogs were lost through anesthesia, shock and sepsis, but after certain lessons had been learned, a series of successful cases followed, in which all the dogs lived and recovered promptly.

In order to judge the rate and character of bone repair in the grafts the dogs were killed at graded intervals after operation, and the series now represents the skulls at two weeks one month, two months, three months, four months and five months after grafting.

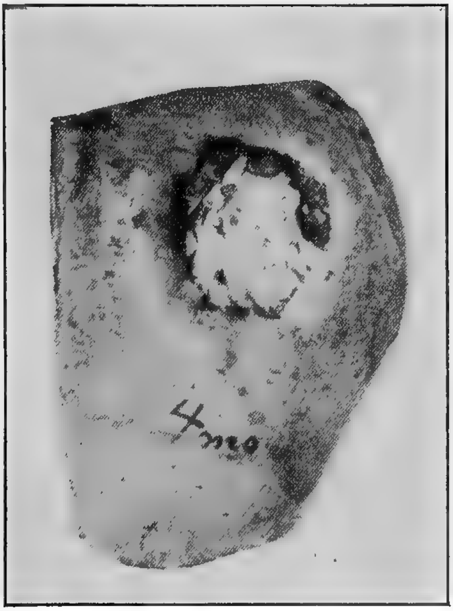

Fig. 6. Skull of dog. External surface showing bone graft four months after insertion.

I wish, especially, to thank Dr. McHenry for assistance in these operations. As in successive cases we alternated as operator and assistant, one half of what has been accomplished in these experiments is due to him.

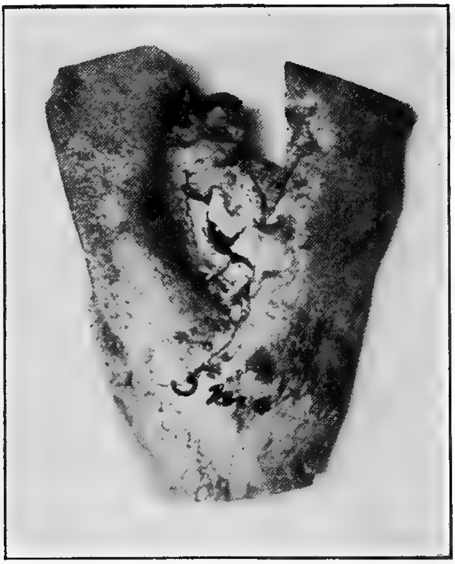

Fig. 7. Skull of dog. External surface showing bone graft five months after insertion.

Summary.

March 17, 1905. Black cur dog. 30 pounds. Graft left side. Single flap. Killed at five months.

March 21, 1905. Brown setter dog. Thirty-five pounds. Graft left side. Single flap. Killed at four months.

March 31, 1905. Coach dog. Forty pounds. Graft left side. Single flap. Killed at three months.

May 3, 1905. Bull dog. Thirty pounds. Graft left side. Single flap. Killed at two months.

Sept. 18, 1905. Bull dog. Twenty-five pounds. Graft left side. Single flap. Killed at one month.

Oct. 2, 1905. Black cur dog. Thirty pounds. Graft left side. Single flap. Killed at two weeks.

I herewith lay before you the skulls of the five dogs operated upon by Dr. Sanford. The specimens were prepared by Dr. Dolley. I am indebted to him for this work and also for the histological sections.

The following description of the sections is by Dr. Dolley.

MACROSCOPICAL APPEARANCE OF EXPERIMENTAL GRAFTS.

In the two weeks dog the graft is movable. This is less marked in the one month dog, and in the rest of the series the graft is firmly united to the peripheral bone. Partial calcification can be detected with a knife point in the two weeks and one month dogs. In the one month and two month dogs, the dura is adherent in several places about the edge of the peripheral bone. Apparently this only occurs with more than usual interval between the graft and the peripheral bone. In the rest of the series the dura is nonadherent in the region of the graft.

MICROSCOPIC.

The tissue was fixed in Zenker's fluid and formalin, and stained with hematoxylin and eosin, and with Von Giesen stain.

TWO WEEKS DOG.

The interval between the peripheral bone and the graft, which is about 2 cm. in the piece taken for microscopic examination, is filled with connective tissue which has undergone a partial calcification. This connective tissue has its origin from the periosteum covering both the superior and inferior surfaces of the peripheral bone and from that covering the superior surface of the graft, from the diploë of the peripheral bone, which in this dog is fairly well marked, and to a slight degree also from the overlying fascia. It has a reticulated appearance with small empty interspaces, irregular in shape, and lined usually with a layer of osteoblasts. Some of the spaces are full of osteoblasts. The connective tissue is faintly fibrillated and very cellular. The cells consist of connective tissue cells proper with fusiform and small spindle nuclei and of osteoblasts. In part the fibrillated character of the connective tissue is lost, and it is homogeneous in appearance. This is more evident about the interspaces just mentioned, and indicates where calcification has occurred. In one block the edges of both the peripheral bone and the graft still remain partially uncovered by cellular periosteum, but in the second, the edge of the peripheral bone is almost entirely covered by osteoblasts, though that of

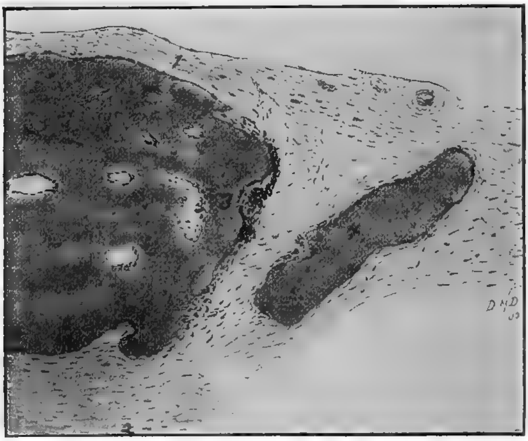

FIG. 8. Edges of graft at two weeks. 1. Superior surface. 2. Inferior surface. 3. Edges of graft. 4. Small bit of graft. (Cam. Luc., Leitz, oc. iv, obj. 3, x 105^3, Zenker's fluid, hematoxylin and eosin.)

the graft is not. Upon the surfaces, and particularly in the diploë of the peripheral bone, the osteoblasts are actively proliferating. The outermost lacunæ of the graft are also filled with osteoblasts. A few osteoblasts lie on the surface of the peripheral bone, but only an occasional one appears on the graft.

ONE MONTH DOG.

In sections from this the most striking feature is the active growth at the edge of the peripheral bone. The new formed bone contains numerous lacunæ, some of which open upon the surface. They are filled with osteoblasts. The free edge is covered with an actively proliferating cellular layer of periosteum. The edge of the graft shows the same appearance of growth but it is not so marked. Lying in the fibrous periosteum on the superior sufrace of the graft proper are several isolated areas of true bone which possess lacunæ and are covered with a layer of osteoblasts. These are probably fragments which were accidentally imbedded at the operation and which remained viable. Their structure is too dense and the bone corpuscles are too few and too contracted for the areas to be new formed bone. As in the two weeks dog, the interval between the graft and the bone, which macroscopically was almost solidly calcified, is composed of connective tissue. It differs from the earlier stage in that it is less cellular, and the interstices are larger and all empty. Judging from the paucity of osteoblasts, there is little absorption of the graft.

FIVE MONTHS DOG.

The graft and the peripheral bone have grown to within $\frac{1}{5}$ mm. of each other but both are still sharply defined. After decalcification, the interval between them is composed of connective tissue whose origin from the periosteum of the superior and inferior surfaces can still be traced, but which has almost entirely lost its fibrillary character between the two edges, being homogeneous, with a few contracted osteoblasts and spindle nuclei. No osteoblasts are seen.

Periosteum covers the edge of both the graft and the residual bone, and in each for a short distance from the edge the appearance is that of newly formed bone, with numerous osteoblasts. The initial process of calcification is evidently being replaced from both directions by true bone.

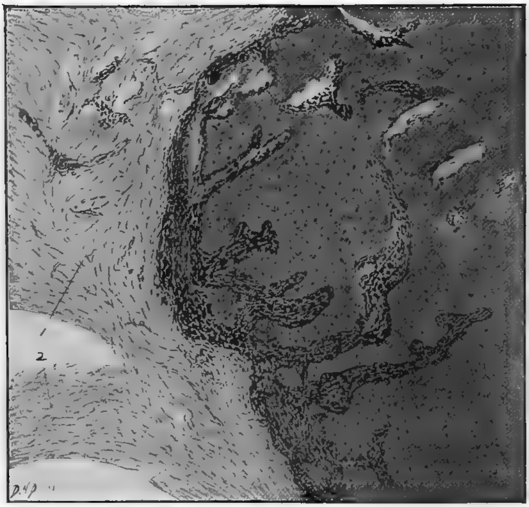

FIG. 9. Edge of peripheral bone at one month. Shows rapid growth of bone. 1. Connective tissue filling gap between edge of bone and edge of graft. 2. Dura mater. (Cam. luc., Leitz, oc. iv, obj. 3 x 105³. Zenker's fluid, hematoxylin and eosin.)

CONCLUSIONS.

1. The initial process is the filling of the gap between the graft and the peripheral bone with connective tissue, which arises principally from the periosteum of each, and which at two weeks has already undergone considerable calcification.

2. The graft remains viable and intact, and begins to grow both in thickness and at its edges.

3. Growth of the free edge of the peripheral bone is more marked than in the graft.

4. The growth of these gradually replaces the initial calcification, and at five months only a trace of the process remains. The probabilities are that after longer time there would be a true bony fusion.

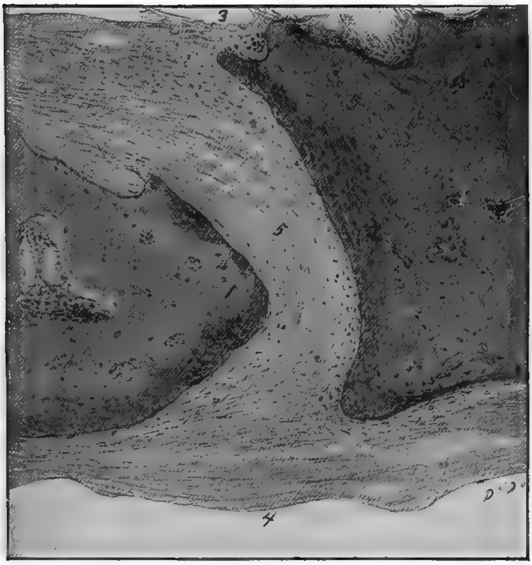

FIG. 10. Edges of graft and peripheral bone at five months. 1. Edge of bone. 2. Edge of graft. 3. Superior surface. 4. Inferior surface. 5. Calcified connective tissue. (Cam. luc., Leitz, oc. 4 obj. 3_1 x 100^3. Formalin, hematoxylin and eosin.)

The final conclusions reached by this paper are:

1. Defects of the human skull can be covered by bone.
2. The bone may be secured from a portion of skull adjoining the defect.
3. This bone graft represents essentially the outer table of the skull, with the periosteum covering it.
4. No pedicle need be preserved in order to insure the viability of the bone graft.
5. Experiments on dogs show the graft to be solid at three months.
6. Histological examination shows that the bone remains viable and grows into its new position.

The object of this paper is to show that defects of the skull should be repaired promptly in order to avoid the occurrence of epilepsy and allied conditions.

Reprint from SURGERY, GYNECOLOGY AND OBSTETRICS, July, 1906

Western Reserve University
Department of Surgery

A STUDY OF INFECTIONS OF THE KNEE-JOINT, AND THEIR TREATMENT[1]

A PRELIMINARY REPORT

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AND

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THE title of the paper which I present to you indicates sufficiently its character. Even a full discussion of the various infections of the knee is more than can be compassed satisfactorily within the allotted time.

In explanation, however, it may be said that during the last two or three years in the service at Lakeside Hospital, an experience has been gathered which has greatly aroused our interest. As a result, we are at the present time following out certain lines of investigation, in the hope that it may be possible to clear up some of the obscure problems which have puzzled us hitherto.

There are numerous cases of inflammation of the knee-joint in which the chief manifestations are swelling with effusion, and pain and tenderness on pressure or motion. To these have usually been applied the name "articular rheumatism." They have usually been sent into the medical wards, and have been treated with salicylates. Some cases have been quickly benefited, while others have pursued a chronic course, and have finally been dismissed with marked limitation of motion, or perhaps with joints still swollen and tender.

Among the cases classed as rheumatism, we have found on investigation a varying ætiology, viz., syphilis, infections of gonococcus pneumococcus, streptococcus, tuberculosis, floating cartilages, both tuberculous and traumatic, besides various cases of chronic synovitis, the cause of which we have been unable to determine.

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[1] Read by invitation before the Academy of Medicine of Philadelphia, March 5, 1906.

We have gathered within a few years something over eighty cases of diseased knee-joints, but it is not until recently that anything like an effective study of these cases has been instituted.

A statistical study of the cases will not be attempted at this time, but selected cases will be utilized for the purpose of illustration.

Before discussing the conditions which may be called autoinfectious, it may be of interest to speak of four cases of infection, treated by incision and gauze packing. Two cases were infections from wounds; one followed gonorrhœa and one exposure to cold.

The history of the cases is as follows:

CASE I. Surgical No. 3248. Admitted Sept. 10, 1902. Discharged Nov. 27, 1902. Male, æt. 41 years, locomotive-engineer.

Family History. Negative.

Previous History. Children's diseases. Gonorrhœa seventeen years ago. Complete recovery.

Present Illness. Five weeks ago, struck left knee with a hatchet, which entered to the bone. Continued work for the remainder of the day. Laid off work for one week, when wound seemed to be healed. Worked second week, when wound opened and discharged a watery fluid. Called a physician. Since then (three weeks ago) knee has been getting worse. Much pus discharged from wound.

Physical Examination. Well developed and nourished man. Heart and lungs negative. Left knee much swollen; tender, especially on the inner side; increase in local temperature. Glands in groin enlarged. Urine normal. Incision above the patella 2 cm. long.

Operation. By Dr. Dudley P. Allen.

Probe, passed into sinus, led directly into joint. The joint cavity was laid open by horseshoe-shaped incision, with convexity upward from external to internal side, passing above the patella. The tendon of the quadriceps extensor divided, the patella reflected downward, and the joint freely exposed. The synovial membrane was roughened, and formed the walls of an abscess cavity. Cavity cleaned out and joint completely packed with iodoform-gauze. Leg dressed in a partially flexed position.

Sept. 16. Under an anæsthetic, packing was removed. Joint found fairly dry, with no pocketing of pus. Packing replaced. Leg dressed in a more extended position.

Sept. 20. Under anæsthetic, packing removed. Joint irrigated with saline. Two small drains of iodoform-gauze inserted, one on each side. Leg dressed nearly straight, in position desired for final result.

Sept. 24. Under anæsthetic, drainage removed. Joint irrigated and drainage replaced.

Sept. 26. Knee redressed without an anæsthetic.

Oct. 20. Packing discontinued. Weight, which had been used to aid in extending the leg, removed.

Oct. 22. Operation by Dr. J. A. Sherbondy.

Under an anæsthetic, the granulating area above the knee, an area 10 x 6 cm. skin grafted by the Thiersch method.

Nov. 11. Entire surface covered with skin. Patient in wheel-chair.

Nov. 22. Patient on crutches. Leg swells during the day, but reduces at night.

Nov. 27. Resting considerable weight on leg, but still wears a Ham splint. General condition good. Discharged improved.

Pathological Report. Streptococci.

Re-examined March 1, 1906. Is working every day as fireman, shoveling many tons of coal. Knee is stiff. Otherwise well.

CASE 2. Surgical No. 5826. Admitted Dec. 12, 1904. Discharged April 15, 1905. Male, æt. 26 years, carpenter.

Family History. Negative.

Previous History. Has had pneumonia.

Present Illness. Six weeks ago, cut himself above the left knee with a chisel. Applied raw beef for four days following. Then the opening was enlarged, cleaned out, and packed. Four or five days later, multiple incisions were made around the knee-joint and packed. Condition improved until two weeks ago, when he complained of tenderness over tibia. Ten days ago the leg was opened and head of tibia was found necrosed. The wound was curetted and packed. Patient has had no rise in temperature the past week, but redness and pain on motion have increased.

Physical Examination. Moderately well developed and nourished man. Pale. Heart and lungs normal. Left leg is in a splint. Above knee are five or six incisions with packing. Joint greatly enlarged, and very tender and painful.

Operation. By Dr. Dudley P. Allen.

A horseshoe-shaped incision was made, passing below the patella and cutting the ligamentum patellæ. Flap containing patella dissected upwards. Patella dissected off. The leg was flexed and knee-joint thoroughly exposed. It was found filled with granulation tissue. All infected tissue dissected and curetted away. The lower end of the femur and upper end of the tibia were found necrotic in spots, the articular surfaces, however, being peculiarly exempt. These spots curetted away. Cavity irrigated with 1 to 5,000 bichloride and packed with iodoform-gauze. Skin flap loosely fastened at its lower extremity with a silkworm-gut stitch. Knee dressed in a flexed position on a Ham splint.

Dec. 21. Under gas, packing removed and replaced.

Feb. 23. Patient up in wheel-chair.

March 15. Sinuses syringed daily with peroxide, and packed with iodoform-gauze saturated with tincture of myrrh.

March 23. Patient on crutches.

April 16. Sinuses very small. Very small amount of drainage gauze.

Re-examined March 1, 1906. Knee stiff. Can do all kinds of work, and walks without difficulty.

April 15. Discharged improved.

CASE 3. Surgical No. 3874. Admitted April 17, 1903. Discharged Sept. 1, 1903. Male, æt. 25 years, clerk.

Family History. Negative.

Previous History. Has had gonorrhœa.

Present Illness. Was admitted five weeks ago to medical service for typhoid fever. Knee commenced to swell, and has been very sensitive ever since. In constant pain. Fluid has been twice aspirated. Fluid shows gonococci.

April 18, 1903. Operated by Dr. Maurice H. Richardson.

An incision three inches long made into knee-joint on inner and outer sides. Fluid and flakes of fibrin escaped. Joint thoroughly flushed with 1 to 2,000 bichloride, followed by saline solution. Plain gauze drainage in both inner and outer wounds. Provisional silkworm-gut sutures inserted.

April 20. Gauze removed and provisional sutures tied.

May 1. Operation by Dr. Dudley P. Allen.

Horseshoe incision below patella and flap, including patella dissected upward. Joint disorganized and contains pus. Joint curetted and packed with iodoform-gauze.

May 4. Under chloroform, dressing changed and knee straightened.

May 7. Dressed without anæsthetic. Considerable discharge of pus-colored green by bacillus pyocyaneus.

Aug. 15. Patient on crutches.

Sept. 1. Bearing some weight on knee; wound entirely healed; swelling and tenderness nearly gone. General condition good.

Discharged cured.

Pathological Diagnosis. Subacute gonorrhœal arthritis.

Re-examined March 1, 1906. Knee stiff; can use perfectly in every way.

CASE 4. Surgical No. 3587. Admitted Jan. 5, 1903. Discharged May 15, 1903. Male, æt. 18 years, laborer.

Family History. Negative.

Previous History. Measles, whooping-cough, and pneumonia.

Present Illness. Three weeks ago, worked for two days standing in water, and at that time had a rash on entire body, resembling urticaria. In two and a half weeks his legs from ankle to knee became red, swollen, painful, and hot. His physician told him he had erysipelas, and later, inflammatory rheumatism. This condition lasted two days. Later, the trouble settled in his right knee and left ankle. He has been gradually improving; the pain is not so great, the swelling less, the movements better.

Physical Examination. Well developed and fairly well nourished. Heart has loud systolic murmur at apex, transmitted to axilla and back; slight enlargement. Lungs normal. Right knee swollen, tender; fluctuating and increased temperature. Left ankle slightly swollen and tender. Urine normal.

Jan. 6. Operation by Dr. Dudley P. Allen.

Under ether, an incision was made into the knee-joint, on the upper and inner aspect. A quantity of pus escaped. Pus could be expressed from the direction of the thigh. The incision was enlarged in a horseshoe-shape to the opposite side, cutting the ligamentum patellæ. Pockets of pus were found in the thigh; accordingly, longitudinal incisions were made anteriorly. Longitudinal incisions were also made posterior to the knee-joint. The cavities were packed with iodoform-gauze. An incision was made above the left ankle. Considerable pus was evacuated. The bone was found denuded of periosteum. Wound packed with iodoform-gauze.

Up to Jan. 24th, wounds packed daily. Considerable discharge. Dressing on alternate days begun.

Jan. 31. Part of packing left out.

Feb. 21. Packing nearly all out, but little discharge.

Feb. 28. All drainage dispensed with.

March 8. Pocket beneath lower end of femur opened spontaneously and pus evacuated. Drained.

May 15. Patient walking on crutches. Slight discharge from lower end of femur and upper end of tibia. No movement in knee.

Discharged improved.

Pathological Report. Streptococcus and staphylococcus pyogenes aureus.

Re-examined March 1, 1906. Knee stiff; can walk perfectly well.

Every one who remembers the preaseptic days knows with what dread such cases were formerly regarded. The advent of antiseptic treatment was inadequate to combat infection in so complicated a joint, and doubtless all of you recall cases in which the most radical drainage and washing of the knee-joint has failed to check infection, and the case has terminated either in amputation or death.

Guided by experiences of this sort, we have at last adopted another method. The knee has been opened by a transverse incision below the patella, and lateral incisions to give free access to the upper portion of the joint. The lateral ligaments have been left intact.

The knee has been flexed, thoroughly washed, and while in the flexed position, every portion of the joint has been packed with iodoform-gauze, care being taken to carry the gauze into the posterior part of the joint, about the crucial ligaments and behind the condyles of the femur. By the flexed position and packing, absolutely perfect drainage is obtained, and the septic absorption ceases. When it has ceased, the gauze is withdrawn, a less amount is reinserted, and as rapidly as possible the leg is straightened. Healing takes place by granulation. By a careful adjustment of the dressings and bandage, and the gradual straightening of the leg, the granulations are covered, and the patients have recovered with a straight leg. Of course the knee-joint is stiff.

Case 2 was of the most desperate character, since the disease was far advanced when the patient was admitted to the hospital. Extensive abscesses formed at various points of the leg. These were incised and drained as they developed, and the final result was most satisfactory.

The results have been such as to encourage us to repeat the treatment in similar cases as they present themselves. By this method, every part of the joint is drained with absolute certainty, whereas by multiple incision with drainage and irrigation, it is extremely difficult to drain the posterior part of the joint. The result is certainly as good as can be obtained by resection of the joint, and the care of the case is less difficult and the relief of sepsis is more certain.

As opposed to this radical method of treatment is an experience of unusual interest.

The history of the case is as follows:

CASE 5. Surgical No. 6663. Admitted Sept. 18, 1905. Dismissed Jan. 23, 1906. Male, æt. 27 years, machinist.

Family History. Negative.

Previous History. Grippe several years ago. Laid up two weeks.

Present Illness. Oct. 31, 1904. Fell from ladder, causing compound fracture of right leg four inches above ankle. In hospital in Indiana until Sept. 8, 1905.

Sept. 15, 1905, was admitted to Lakeside Hospital. About one week before admission, leg became inflamed, opened, and discharged pus.

Physical Examination. Patient in poor general condition. Heart and lungs negative. Urine cloudy; specific gravity 1012; acid; faint trace albumin; sugar absent; few leucocytes and epithelium; few granular and hyaline casts. Right leg showed a compound, ununited fracture about one inch above ankle. It was swollen, much inflamed, and there was a thin, yellow, purulent discharge.

Sept. 19. Left foot and ankle considerably swollen, and on examination the left knee-joint found to be much distended with fluid.

Sept. 21. Left knee was aspirated, and 3 ounces greenish yellow fluid was obtained. Joint was washed with 1 to 40 carbolic acid, and injected with 2 ounces iodoform emulsion containing 30 grains iodoform. Fluid produced pure culture of streptococcus.

Sept. 25. Swelling much diminished. The temperature on Sept. 21st was 103° F. Pulse 110. No essential change in temperature or pulse.

Sept. 26. Antistreptococcus serum 10 c.c. injected every four hours until Oct. 6th. Had marked rash following injection of serum.

Oct. 6. General condition improving.

Oct. 24. Right leg amputated. Healing per primam.

Oct. 29. Began baking left knee daily, carrying temperature to 330° to 350° F.

Jan. 23. Discharged. No pain. Knee almost normal. Walks well on crutches. Still a little grating in joint. Could flex knee almost to right angle.

The complications in this case were unusual. The patient was markedly septic; there was evidence of kidney involvement, as shown by the presence of albumin and casts in the urine. Amputation of the fractured and septic leg, leaving a knee-joint on the opposite side infected with streptococcus, would probably have proved fatal; a similar result would probably have attended an operation on both leg and knee at the same time, nor could much have been expected from any operation on the knee leaving an infected fracture.

The result following aspiration and injection of the knee-joint surpassed our highest anticipations, since the case appeared wellnigh hopeless by any method of treatment. After the condition of the knee had improved, the fractured and infected leg was successfully amputated. When the patient was dismissed from the hospital, he was walking upon crutches and the infected knee-joint could be flexed to right angle, and was free from pain and tenderness. In other cases of infection of the knee-joint, when the conditions are not urgent, and the patient's life does not seem to be endangered, we shall be tempted to repeat this treatment.

The question naturally arises, Will other pyogenic organisms be similarly affected by it. Our experience is too limited to warrant us in drawing any conclusions.

That autoinfections with pyogenic organisms may be extremely virulent is evidenced by the following case:

CASE 6. Surgical No. 561. Admitted Jan. 24, 1899. Died Feb. 6, 1899. Female, æt. 40 years, dressmaker.

Family and Previous History. Not obtainable.

Present Illness. Four days ago consulted physician for stomach and bowel trouble. The following day left knee began to pain. She was given salicylates, and felt better. Next day she asked for crutches to get about.

Physical Examination. Fairly well developed and nourished. Heart normal. Left knee-joint greatly distended. Fluctuation distinct. Pain on manipulation. Local temperature raised. Skin slightly reddened. Flexion limited. Enlarged glands in left groin. Lungs: Right infraclavicular space slightly higher percussion note, increased respiratory murmur and vocal fremitus; no râles. Abdomen negative.

Jan. 25. Knee aspirated and pus withdrawn. Immediate operation. The knee was freely opened by incisions on each side of the patella, and posterior to the condyles. The joint was filled with cream-colored pus. The cavity was flushed with sterile water and drained with plain gauze. The two days following, the patient was delirious.

Jan. 27. Amputation of thigh through lower third. Wound drained with iodoform-gauze.

Feb. 2. A few granular casts in urine.

Feb. 3. Two stitches were removed from stump, and about 3 ounces seropurulent fluid escaped. Wound flushed daily with boracic acid solution. Wound unhealthy. White-blood count, 27,000. Patient steadily grew worse, was very restless and delirious at times. Pulse and temperature rose steadily.

Died Feb. 6, 1900.

Pathological Report. Pneumococcus in pure culture.

Autopsy. Chronic fibroid apical tuberculosis. Œdema and congestion of the lungs. Cloudy swelling of the heart muscles. Fatty degeneration and cloudy swelling of liver and kidneys. Hemorrhagic infarct of spleen. Uterine myomata. Amputation wound middle third left thigh.

Cultures from stump, diplococcus lanceolatus, and staphylococcus aureus.

What would have been the result had treatment been instituted earlier is, of course, problematical. It would seem quite possible that it would have been more effectual.

On further study it may be found that certain infections are amenable to treatment by aspiration and injection; that others may be treated by incision of the joint and packing with iodoform-gauze, while in other cases, nothing will suffice but amputation.

One conclusion is inevitable; viz., that when doubt exists as to the nature of a joint inflammation, aspiration should be practised in order that the character of the infection may be established as quickly as possible. With early diagnosis it may be possible in certain classes of pyogenic infection to aspirate, wash, and inject joints, and thus to secure entire relief. In other cases, incision and packing may be necessary.

The subject of tubercular infection of the knee is most complex. Richard Volkmann published, over twenty years ago, in the *Klinische Vorträge*, an article on joint tuberculosis. With this were a number of beautifully colored plates to illustrate the position that joint tuberculosis is usually primary in the bones, and that the joint becomes involved only secondarily. Undoubtedly this is true in a large number of cases. Several times in my clinic, during the resection or erasion of a knee-joint, I have pointed out that no involvement of bone could be found after careful search, only to find, when about to close the operation, that the curette slipped into a bone cavity, probably the starting-point of the disease. Several times, by the enlargement of the inner condyle of the femur, with the consequent genu-valgum, I have diagnosticated tuberculosis of the condyle without joint involvement, and by means of an extra-articular incision have opened and evacuated a tubercular deposit.

Huntington of San Francisco has done the same thing for tuberculosis of the head of the femur by means of an opening through the trochanter major.

Doubtless the X-ray will aid us materially in the diagnosis of such cases. Personally, I have not met a case of the sort since I have had a thoroughly efficient Röntgen apparatus at my disposal.

Unquestionably, such cases are very rare. They are not, however, on this account to be overlooked. The common cases of tuberculosis, whether primary in bone or not, usually show synovial involvement early in their history. The uncertainty of diagnosis usually leads to the treatment of such joints by what is called the conservative method of rest, counter-irritation, plaster bandages, etc. To be sure, some cases may be relieved and others cured by such methods. In cases in which we have suspected tuberculosis, it has been our custom of late to aspirate the joint and fill it with an emulsion of iodoform. The results have been quite satisfactory. A great encouragement to this method of procedure has been the results obtained in psoas and iliac abscess treated by a similar method. We now have a considerable number of seemingly hopeless cases of psoas and iliac abscess treated by aspiration and injection of iodoform. In some cases we have *aspirated* and *injected* four or five times, while in other cases the operation has been repeated as many as ten times. The patients have recovered, and are alive and seemingly in perfect health after years. The efficiency of the method has led us to adopt it in other conditions, and the results in the knee-joint have proved very encouraging. Unfortunately, it is often difficult to establish positively the diagnosis of tuberculosis, since the cover-slip preparations obtained by aspiration do not show bacteria of any kind, and the inoculations of guinea-pigs have not induced tuberculous infection. Although we have injected with iodoform a considerable number of tuberculous knee-joints, we have not been able, in the short time at our disposal in preparing this paper, to look up the cases with sufficient thoroughness to report the end results. The impression made upon us by our experience thus far is, that in cases of what we have diagnosticated as tuberculosis, injections at a fairly early stage, before the disease is far advanced, are decidedly beneficial.

Of late, encouraged by the impunity with which we have opened the knee-joint in many cases, we are beginning to question if it is not wiser to resort to early incision in cases suspected of being tuberculous.

In a recent case of effusion into the knee-joint, unattended with much pain or tenderness, a movable body could be felt. This was removed. On microscopic section this body was found to contain typical giant cells, and the condition was unquestionably tuberculous. The history of the case was as follows:

CASE 7. Surgical No. 5636. Admitted Jan. 5, 1905. Discharged Feb. 15, 1905. Female, æt. 20 years, negress, housewife.

Family History. Negative.

Previous History. Children's diseases. Typhoid fever five years ago.

Present Illness. Five years ago, one month after getting about after typhoid fever, she had pain and swelling in left knee. Swelling reduced at times by liniment, but would reappear. Two months later, left wrist became swollen and painful. For past five years, condition steadily grew worse. For past year, elbow has also given trouble.

Physical Examination. Well developed and nourished. Left knee is slightly swollen, circumference 15 inches; right knee 13½ inches. Swelling is general, but most noticeable on outer side, above and below the patella and at the inner condyle. Flexion painful beyond 75 degrees. Swelling soft, but no distinct fluctuation. Left wrist slightly swollen, especially on flexor surface. Circumference one half inch larger than right, movements through arc of about 30 degrees. Slight pain on pressure and manipulation. Left elbow slightly painful on internal condyle. No limitation of motion.

Jan. 13. Operation by Dr. Dudley P. Allen.

Incision on inner side of knee, over an apparently foreign body, and joint opened. One half-ounce amber fluid escaped. A piece of cartilage was found nearly free, but attached on the inner side of the knee to the parietal wall of the joint cavity. It was excised, and measured 3 x 3 x 1 cm. Several small, white, tongue-like bodies were found free or loosely attached. The synovial membrane appeared inflamed. Cavity irrigated with 1 to 40 carbolic, filled with iodoform emulsion, and capsule sutured with catgut and skin with silkworm gut. Ham splint. Left wrist injected with iodoform emulsion under pressure.

Jan. 24. Knee still swollen.

Operation. By Dr. Dudley P. Allen.

Knee-joint aspirated, but very little fluid obtained. Injected with 2 ounces iodoform emulsion. Needle puncture closed with catgut stitch.

Feb. 15. Knee much better; can walk about on it with little pain or difficulty. Wrist still painful.

Pathological Report. Mass of tissue. Color, pale yellow to pink. Where the color is yellow, it feels like cartilage. The surface is smooth and shiny. Cover-slip and culture from fluid show no bacteria.

Microscopically. Material is infiltrated by many round cells, which, in places, have undergone necrosis and formed tubercles, many of which contain giant cells.

Feb. 25, 1906. Mother says daughter's lameness is scarcely noticeable. Walks without pain. Occasionally, slight swelling with slight pain in damp weather. Greatly improved in every way. Wrist absolutely well.

This and similar experiences lead us to question if a more radical method of procedure is not a wise one.

In doubtful cases, why is it not wise to incise a joint, obtain material for cultures, microscopical section, and animal inoculation, and at the same time apply to the interior of the joint the treatment seemingly best suited to it, whatever condition is found to be present?

Thus far, in certain cases thought to be tuberculous, we have filled the joint with an emulsion of iodoform, seemingly to the great benefit of the patient. Since the adoption of this method the time has been too short to give final results, since, as you all know, tuberculous knee-joints, seemingly cured, may give trouble after many years. I may say, however, that the results, so far as rapid improvement and mobility are concerned, seem much superior to the older methods of counter-irritation, rest, etc. One thing is certain, and that is, that no ill effects have followed the method. If early diagnosis were the only advantage, this would certainly be a decided gain.

The physical appearances of a joint are often inadequate to a positive diagnosis of tuberculosis until the disease has existed for a considerable time. Aspiration, too, even when tuberculosis is present, may fail to secure bacilli or fertile cultures. Diagnosis by means of animal inoculation is not always successful. Tuberculin as an aid to diagnosis has not proved itself to be satisfactory in our hands.

The uncertainty of these methods of diagnosis is apparent from certain cases in which cover-slip preparations showed no bacteria, and in which cultures were sterile, while microscopic sections gave positive evidence of tuberculosis.

Certainly, free incision of the knee-joint offers the best opportunity for diagnosis. It permits the most radical treatment at an early stage of the disease, and, as a consequence, the results to be obtained are more promising. Guided by our observations thus far, we shall certainly pursue this method of treatment further.

The use of the X-ray has been spoken of as an aid to diagnosis. As a routine method it seems desirable. Besides giving information concerning the condition of the articular surfaces, it may reveal the presence of floating cartilages. These floating cartilages may be not only of traumatic, but also of tubercular origin, and are often associated with a considerable amount of fluid in the joint.

Another class of cases of the greatest seriousness, often difficult of diagnosis, and of frequent occurrence, are the cases of gonorrhœal rheumatism. Many joints may be affected at the same time, but, without having gathered statistics, my impression would be, that the knee-joint is the one which most frequently gives grave trouble, and is the one permanently impaired oftener than any other. The diagnosis is usually acute articular rheumatism, and the treatment corresponds to the diagnosis. A careful investigation of the history of the case will usually throw light upon it. Fluid obtained by aspiration may give characteristic cover-slip preparations, as shown in case 9, but, unfortunately, this is not always true.

We give the histories of two cases.

CASE 8. Surgical No. 4999. Admitted May 20, 1904. Dismissed June 10, 1904. Male, æt. 29 years, machinist.

Family History. Negative.

Previous History. Tuberculous hip. Gonorrhœa two months ago. Still discharge.

Present Illness. Five days ago, sudden pain and tenderness and swelling in left knee. Pain and swelling increased rapidly.

Physical Examination. Poorly nourished. Body covered with scabies. Urethra shows glairy discharge. Left knee swollen, tender, fluctuating, some redness, great limitation of motion. Holds knee in flexed position. Right leg atrophied and six inches shorter than left leg. Scars about right hip. Heart and lungs normal.

May 21. Operation by Dr. Dudley P. Allen.

Aspirated; several ounces bloody, purulent fluid removed. Washed with carbolic 1 to 40; injected with iodoform and glycerine 1 ounce.

Intense pain. Gave morphia.

June 10. Fluid gone. Still some tenderness over head of tibia. Discharged improved.

Pathological Report. Cover-slip and culture negative.

Feb. 26, 1906. Doctor reports patient perfectly well.

CASE 9. Surgical No. 6522. Admitted Sept. 22, 1905. Dismissed Dec. 1, 1905. Male, æt. 18 years, laborer.

Present Illness. Admitted to medical ward ten days ago. For six days before entrance, right foot and ankle have been painful and swollen. Some pain for a week previous.

Physical Examination. Joints involved are right elbow, right knee, right and left ankle. Swelling, redness, pain, tenderness. Right knee contains considerable fluid, and is painful on motion. Aspirated in medical ward, and gonococci found in fluid.

Sept. 26. Operation by Dr. R. W. Elliott.

Right knee aspirated and 11 ounces greenish fluid, containing fibrin flakes, removed. Cavity washed with 1 to 40 carbolic-acid solution and injected with 2 ounces iodoform emulsion.

Nov. 27. About on crutches. No pain in joints. Right knee occasionally swells slightly, and is slightly rigid. Discharged improved.

We have been employing aspiration, and washing with carbolic-acid solution, followed by the injection of an emulsion of iodoform in glycerine, in an increasing number of cases. Seemingly, joints thus treated have improved more rapidly than others. It is true that with gonorrhœal infection of multiple joints, some recover without treatment. This observation would seem to throw doubt upon the necessity of any radical treatment. I think, however, every surgeon has seen numerous knee-joints stiff from infection. My own observation is that the knee is the joint most seriously affected, and consequently the one most demanding radical treatment, and it is our purpose to pursue this method of treatment further.

Having now considered joint infections the result of syphilis, tuberculosis, trauma, autoinfection, and gonorrhœa, there remains the class of cases known as acute articular rheumatism. We do not, in this paper, consider chronic rheumatic arthritis, gout, etc. The question arises, What is rheumatism? The similarity which it bears to certain joint infections suggests that it may also be an infection. Many cases yield to treatment by the salicylates. In not a few, the enlargement of the knee-joint remains for an indefinite period, and motion is much impaired. It is cases of this sort which are especially interesting for study. We record three cases in which we have widely incised the joint and treated it with 95-per-cent carbolic acid. In case 11, the joint was poured full of the acid; this was allowed to remain while the joint was flexed and extended several times, and the joint was then thoroughly washed with 95-per-cent alcohol. The applications were immediately repeated. It is interesting to notice that while this method was applied to one knee, the other knee was washed out with a solution of carbolic acid in water 1 to 20. The knee treated by injection suffered considerable pain. That treated by incision and the application of carbolic and alcohol suffered almost no pain. The histories of the three cases are as follows.

Case 10 is too recent for a statement of result, except so far as the immediate condition is concerned.

CASE 10. Female. Admitted to medical ward Jan. 29, 1906.

Family History. Negative as to tuberculosis, cancer, rheumatism, heart and kidney disease.

Previous History. Always well. Never had rheumatism, typhoid fever, or any other contagious disease. Habits good.

Present Illness. Three days before admission to hospital, patient, on arising in the morning, felt dizzy, and had slight pain in right knee, which became more severe before evening. This same evening, patient noticed that the left knee and the right shoulder had become slightly painful. The following day patient had sore throat. Pain in joints more severe. Some chilly sensation. Some perspiration. On admission, temperature 101.6°. Respiration 25. Pulse 125.

Physical Examination. Patient well nourished. Skin clear. Tongue coated. Throat reddened; right tonsil enlarged, with few white patches upon it. Chest large and well formed. Lungs negative. Both knees somewhat swollen; surface temperature increased. Motion painful.

Jan. 30. Both wrists are now swollen. Patient made toxic with sodium salicylate. Lead and opium stupes applied.

Feb. 5. Knees strapped with adhesive and put in pillow-slips, which soon had to be removed.

Feb. 9. Considerable fluid in knees, as noticed by floating patella. Aspiration of right knee gave few cubic centimeters sterile fluid; left knee, none. Knees painted with iodine.

Transferred to surgical ward Feb. 19th. At this time the swelling in the wrists had disappeared.

Operation Feb. 19th. At first one ounce of bloody fluid was removed, and then, on pressure, a thick sanguinous fluid, containing many flocculent masses, was obtained. The joint was then thoroughly irrigated with 5-per-cent carbolic acid. A suture of silkworm closed aspiration wound. Dressings and posterior Ham splint applied.

Left knee: Longitudinal incision, 10 cm. long, was made external to patella, and knee-joint was fully exposed. The articular surfaces of the joint appeared normal. The synovial membrane lining capsule of joint cavity was very markedly thickened, of a dark purplish color. Fringes much hypertrophied. Several ounces of dark thick sanguinous fluid escaped. The joint was thoroughly irrigated twice with 95-per-cent carbolic acid, followed each time with 95-per-cent alcohol and sterile water. Capsule of joint sutured with plain gut. Skin incision closed with silkworm gut. Dressings. Posterior Ham splint.

Pathological Examination. Granulation tissue showing subacute inflammation.

Bacteriological Examination. Fluid from right knee slightly bloody, with white flakes, and few fibrinous strings. Cover-slip preparation failed to show organisms.

Cultures in bouillon and on blood serum failed to show a growth after 72 hours in incubator at 37.5° C. temperature. Guinea-pig injected with 2 c.c. fluid intraperitoneally still living.

Fluid from the right knee, taken when joint was opened, is of straw color, slightly opalescent, thin and watery in consistency. Cover-slips failed to show organisms, only a few round and polymorphonuclear and red-blood cells being found. Cultures in bouillon and on blood serum remained sterile after 72 hours in incubator at 37.5° C. A guinea-pig was inoculated intraperitoneally with about 2 c.c. of fluid. Death within 24 hours.

Autopsy showed a slightly congested peritoneal surface, with slight serous exudate. Liver and spleen slightly injected. No other findings. Cover-slips showed a few cocci in one or two round cells, but they were not numerous enough to demonstrate whether or not they stained by Gram's method.

Cultures in bouillon, glucose agar stab, and on blood serum failed to show the slightest growth in seventy-two hours. Cause of death probably toxæmia.

Pathological sections were made from exuberant tissue above joint over the femur, and from below joint over the tibia. These were fixed in both formalin and in alcohol, and all show practically the same condition. The lining of the joint cavity is covered with a thin layer of fibrinous exudate containing a few round cells. Beneath this is a zone 2 to 4 mm. thick, composed of highly inflammatory tissue. There are many newly formed blood-vessels with thin walls and capillaries, and the tissues between these is of a loose reticular nature, and markedly infiltrated with small round cells with a fair proportion of plasma cells, a few eosinophiles, but not many polynuclear leucocytes. Beneath this zone the vessels are larger, and distended with blood. The deeper tissues are largely fat. A Gram stain of tissue failed to show organisms in or on tissue.

Diagnosis. Intense congestion. Subacute inflammation of synovial membrane.

May 10, 1906. Since reading the paper in Philadelphia, the progress of the case has been extremely tedious. On the left side, that in which the knee was incised, there was a thrombosis of the popliteal vein, with swelling of the leg below the knee. Both knees have been extremely tender, but now are free from pain, but the joints are stiff. Both knees were flexed one week ago, under anæsthetic, and massage is being employed. One week later there is a decided gain in motion of both knees.

CASE 11. Surgical No. 5367. Admitted Oct. 13, 1904. Dismissed Nov. 7, 1904. Male, æt. 40 years, livery-man.

Family History. Negative.

Previous History. Children's diseases. For years has had frequent micturition, passing large amounts of urine. Often feels weak and dizzy, and vision becomes darkened.

Present Illness. Two years ago, while working on street-car, noticed that his right knee would pain him, especially at the back. Has noticed this pain off and on ever since. One week ago, had pain in back and knee-joint. Has been working up to two days ago. Four days ago, first noticed swelling.

Physical Examination. Heart, lungs, and abdomen normal. Right knee red and discolored from iodine. It is moderately swollen, circumference 8 cm. greater than left. Slight atrophy of the calf. Patella floats.

Nov. 4. Operation by Dr. Dudley P. Allen.

Joint aspirated. A small amount of fluid obtained, irrigated with 1 to 40 carbolic acid, and injected with iodoform emulsion 1 ounce to 30 grains. Splint.

Nov. 7. Knee better, but can walk but little without assistance. Discharged.

Pathological Report. Cultures sterile.

Left hospital Nov. 7th.

Nov. 12. Knee has been getting worse. Has been on feet considerably. Effusion in the joint, and pain.

Nov. 13. Operation, aspiration. Washed with 1 to 20 carbolic, and injected with iodoform emulsion. Splint.

Nov. 27. Splint removed.

Dec. 16. Fluid still present. Operation, aspiration. Washed with 1 to 20 carbolic, and injected with iodoform emulsion 1 ounce. Splint.

Jan. 10. No fluid. Slight pain on complete flexion. Discharged improved.

Re-entered hospital Jan. 30th. Pain, limitation of flexion, and floating patella.

Operation by Dr. Dudley P. Allen.

Aspiration, 2 ounces clear fluid removed, irrigated with 1 to 20 carbolic, injected with 1 ounce iodoform emulsion.

Feb. 15. No effusion. Flexion limited and painful.

March 22. Re-entered hospital. Knee swollen; local temperature increased. Fluid and crepitus.

March 31. Aspiration by Dr. R. W. Elliott. No fluid obtained. Injection with iodoform emulsion 3 ounces.

April 15. Discharged improved. Walks with crutch.

May 14. Re-entered hospital with pain and swelling of right knee. Given sodium salicylate and potassium iodide, and knee baked.

June 3. Operation by Dr. Dudley P. Allen.

Incision 12 cm. on inner side of knee. On opening the capsule, some bloody fluid escaped. The under surface of the patella and end of femur were very rough and soft; the synovial membrane could be peeled off. Joint swabbed with 95-per-cent carbolic, followed by washing with alcohol and saline solution. Capsule sutured with catgut, and skin with silkworm gut. Splint.

June 10. Stitches out. Incision healed.

June 16. Swelling subsided. Knee the same size as left.

July 16. Does not complain of knee. Foot is slightly swollen.

July 25. Knee only slightly painful. Walks with crutches. Discharged improved.

Re-examined Feb. 23, 1906. No pain in knee. No fluid. Walks with cane. Troubled only in walking upstairs. Can flex knee to right angle without pain.

CASE 12. Surgical No. 6533. Admitted Sept. 28, 1905. Dismissed Dec. 6, 1905. Male, æt. 42 years, longshoreman.

Family History. Negative.

Previous History. Typhoid fever 28 years ago. No venereal disease. Alcohol to excess.

Present Illness. Four days ago, sudden pain in knee-joint, which caused him to fall. No known injury, but patient was intoxicated at the time. Has stayed in bed since.

Physical Examination. Patient well developed and nourished. Heart and lungs normal. Abdomen normal. Right knee larger than left. Slight local temperature and floating patella. Slight general tenderness, but no special point of tenderness. Muscles on the back of knee somewhat rigid. Little pain, except on complete flexion.

Oct. 20. Has been treated by rest and pressure, but fluid persists. No general symptoms.

Operation. By Dr. Dudley P. Allen.

Incision into joint on the inner side of the patella. In the synovial membrane is a transverse abrasion one inch long, with ragged edges. The synovial membrane was markedly inflamed. The joint cavity was swabbed with 95-per-cent carbolic acid, and followed by alcohol and flushed with saline. The incision was closed with silkworm-gut sutures. Splint.

Oct. 25. Feeling comfortable. Has had no pain.

Nov. 2. First dressing. Wound healed per primam. Stitches removed.

Nov. 27. Patient on crutches. Some motion in knee.

Dec. 6. Knee slightly stiff, but patient walks without crutches. Dismissed.

Feb. 26, 1906. Re-examined. Patient can now walk everywhere without pain. Knee is normal in size and appearance. Patient can flex leg about 35°, by proper treatment. It is evident that this could be very greatly improved.

Whether further observation of cases such as those last described will result in a positive diagnosis of the cause of inflammation is uncertain. One thing is beyond question, and that is, that, in the cases we have observed, especially case 10, the thickening and congestion of the synovial membrane have been extreme, so great, in fact, that recovery without grave impairment of motion has seemed impossible. The results in cases 11 and 12 are certainly most encouraging, and are such as warrant a further trial of the method.

As we bring the immature suggestions of this paper to a close, we must beg your indulgence. The time at our disposal has been too short to permit the following of many of the cases. Thus the end results can be given in but a limited number. What has been presented is in the line of suggestion. A much longer time and many more observations will be required to establish any positive conclusions.

One conclusion, and only one, seems to us to be established, and that is, that the knee-joint, when infected or inflamed, is not to be considered as a closed cavity to be left alone. Our experience shows that it may be aspirated, injected, or incised with safety, no accident having followed any of these procedures.

The advantages of the radical method are, certainty of diagnosis at an early period, and positive treatment at a time when it may prove efficacious.

Consideration of the Bier method of treatment has purposely been omitted in this paper, since, although the method is now being tried at Lakeside Hospital, our experience with it is too recent and too limited to permit of a discussion of the merits of the method, in comparison with those here suggested.

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Western Reserve University
Department of Surgery

SUBCUTANEOUS INJURIES OF NERVES

WITH A REPORT OF SIX CASES

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IT has long been known that the functions of a nerve trunk may in certain cases be restored, if its cut ends be brought together either immediately after an injury or after an interval of time has elapsed. Thus the problem presented by simple division of a nerve by an open incision is a simple one. On the other hand, in traumatic paralysis from subcutaneous injuries, such as follow fractures and crushing injuries, and in cases first seen after an interval of time has elapsed since the original injury, a number of perplexing questions are at once presented, to the solution of which the modern text-book offers very little accurate information.

The questions which immediately confront one in the treatment of such cases are: What is the exact nature of the injury? Has the nerve been torn, completely severed, or are the symptoms due to the effects of contusion? How long a time should elapse after traumatic paralysis of a nerve before operation for its relief should be urged, and what guides, if any, have we to aid us in deciding this question? How long a time after injury may we promise any result from operative relief, and how much hope of improvement may we hold out in such cases?

It is hoped that a consideration of the following six cases of musculospiral injury, together with some of the other cases already reported in the literature, will aid somewhat in answering the above questions.

CASE 1. Mrs. W. L. R., aged 32, housewife, sustained a badly comminuted fracture at the junction of the middle and lower thirds of the right humerus. At the time of my first examination there was marked swelling of the whole arm, showing evident extensive laceration of the soft parts. A few days after the fracture was set, complete wrist-drop, with inability to extend the wrist or fingers, was noted, together with loss of sensation over the back and radial side of the forearm, corresponding to the skin area, supplied by the musculospiral nerve. Three weeks after the injury, the first evidence of returning sensation was recorded, and from then on the improvement was steady until perfect recovery of sensation at the end of three months. The last skin area to recover was that over the back of the thumb and first metacarpal. Twelve weeks had elapsed before there was any evidence of returning motor control, and fully a year before there was complete restoration of function. Four months after the injury, the patient had about one half the normal power of extension of the wrist, with inability still to extend the proximal phalanges.

During this time, of course, the improvement had been very slow, and hard to perceive from day to day, and the anxiety of the patient was aroused as to how much further improvement could be expected, and at the end of what period we could say definitely that the restoration of function had reached its limit. To decide this question, a neurologist and a surgeon, both of international reputation, were called in as consultants. After a careful examination, they advised operation, on the ground that so long a time had elapsed since the injury, that no further recovery could probably be expected without operation, while an open incision might disclose that part of the nerve had been cut, or that it was being pressed upon by the bony callus, and surgical relief of such a condition might complete the recovery.

The final decision of the matter was left to me, and I took the responsibility of advising a continuance of expectant treatment, for the following reasons.

In the first place, there had been a steady improvement from week to week, from the time the motor function first began to return. To be sure, this had seemed very slow, but I could not make up my mind that it had come to a standstill. Furthermore, I had just read Bowlby's report of a similar injury, in which, there being no motor improvement up to three months after the injury, operation was performed, and a perfectly normal-looking nerve found. One month later, the motor power began to return, and was perfect fourteen months after the injury. I was able to find one other similar case in the literature, and these reports influenced me to delay any operative procedure for some weeks longer. As has already been stated, the outcome of the case completely justified this decision, for at the end of a year function was completely restored.

CASE 2. E. R., Austrian, aged 39, sustained a transverse fracture of the right humerus at the junction of the middle and lower thirds, from a crushing injury. There was immediate motor paralysis of the muscles supplied by the musculospiral nerve, giving the typical wrist-drop, and complete loss of sensation over the skin of the forearm supplied by this nerve. One week after the injury, beginning return of sensation was noted in the forearm, and sensory improvement was continuous from that time on, being practically normal at the end of eight weeks. Five weeks from the date of the fracture, union of the humerus was firm and all apparatus was discontinued.

Although there was still absolute motor paralysis, the fact that sensory impairment had practically recovered gave me confidence that I had to deal simply with a contused nerve, and that a few weeks would show a beginning return of motor power. This expectation was justified by the appearance of the first evidence of motor power, ten weeks after the accident. The return of muscular power was not complete until fully ten months after the injury, but after five months the patient was able to do hard, muscular labor, apparently as well as ever. As in the preceding case, so in this one, the last motion to return was that of lifting the fingers when held in the piano-playing position; i. e., complete extension of the proximal phalanges.

CASE 3. John R., aged 24, farmer, consulted me for pain and numbness of the left forearm with partial wrist-drop, which he stated was gradually increasing. I learned that, three months before, he had sustained a fracture of his left humerus, which had united firmly at the end of six weeks. Shortly after the splints were removed, he began to have pain shooting down the back and radial side of the forearm into the thumb and back of the hand. This was followed by gradually increasing loss of the power to extend his wrist and fingers, and beginning wrist-drop. Massage, passive motion, and faradism were ordered by his physician, and he was told that a few weeks would suffice to rid him of these symptoms.

Examination showed considerable atrophy of the muscles of the left arm and forearm. A moderate sized callus was easily felt about two centimeters below the middle of the humerus, which was somewhat tender on pressure over the inner side of the arm. Over the radial side and back of the forearm, response to sensory stimulation was slow, and the patient complained of a feeling of numbness over this area. The wrist was held in a position of half-flexion with the fingers partly flexed. By great apparent effort the patient was able to straighten the fingers, but not to extend them at the metacarpophalangeal joints, nor could the wrist be extended more than five degrees. It was quite apparent that the musculospiral was involved in the callus of the humerus, and was being pinched as the new bone became denser. Operation was advised, and accepted by the patient. The musculospiral was exposed below the bony callus, and being followed upward, was found to be completely surrounded by new bone. This was chiseled away and the nerve released. At the site of its bony imprisonment, an annular depression was found in the nerve, about one half-centimeter wide, narrowing the nerve to about two thirds its normal size. The nerve was pulled away from the bone, and held by a catgut stitch in the substance of the adjoining muscles.

Complete relief from pain followed immediately after the operation, and ten days later the sensory function was apparently perfect. No gain in motor power was noticed until five weeks after the operative procedure, but from that time on motor improvement was steady until complete recovery six months later.

Case 4. Louis E., aged 31, millwright, caught his left arm in a hydraulic press, the upper edge of the press passing across the arm just below the middle, and the lower edge across the forearm about ten centimeters below the elbow. There was no abrasion of the skin, but very marked laceration of the muscles and subcutaneous tissues. The arm was put at rest, and moist alcohol and boric-acid dressings applied. Five days after the injury, the swelling and œdema were very marked, extending from the shoulder down to the wrist. At this time it was noted that there was marked wrist-drop, with inability to extend the wrist and fingers, and there was a slow response to sensory stimulation over the area supplied by the musculospiral. The power to flex the wrist and fingers was also noticeably weak. These symptoms were regarded at the time as probably due to extensive laceration of the muscles, with possibly some contusion of the nerves, especially the musculospiral. On the eighth day there was distinct redness, tenderness, and induration along the course of the brachial vein, a still greater increase of the swelling of the part, and a temperature of 103.5° F. About two centimeters above and below the internal condyle of the humerus, small incisions were made down through the deep fascia, giving vent to about three ounces of thick chocolate-colored fluid, with bits of muscle tissue in it. A culture taken at the time showed staphylococcus aureus in pure culture. Following these incisions, the swelling of the arm rapidly subsided, but the induration and tenderness along the brachial vein were not entirely gone until five weeks after the accident. Three weeks after the injury it was noted that there was complete wrist-drop, entire loss of the extension of the wrist and fingers, and lack of sensation over the area of the forearm and hand supplied by the musculospiral nerve. At the end of six weeks, the incisions having perfectly healed, and all evidence of the brachial phlebitis having disappeared, an incision was made over the musculospiral, and the nerve isolated and found to be almost completely severed at the level of the upper limit of the pressure exerted by the hydraulic press. A very fine filament about the size of heavy silk, possibly made up entirely of nerve-sheath, held the divided ends together, there being a gap of fully one sixteenth of an inch between the remaining portion of the two ends. The ends of the nerve were trimmed, united with fine silk sutures, and the skin wound closed.

Two days after the operation the patient declared that there was some sensation to touch over the previously anæsthetic area, and this response to stimulation of the skin varied from day to day, now more, now less, up to about the eighteenth day, from which time onward there was constant improvement. The first return of motor power was noted about twelve weeks after operation, and had practically returned to normal about fourteen months later.

Case 5. Anton S., aged 19, laborer. Six weeks before consulting me, he had received a punctured wound from a hot wire through the fleshy part of the inside of his right arm. The wound had suppurated, requiring dressings for four weeks after the accident. Examination showed a small scar about six centimeters above the inner condyle, on the inner surface of the left arm. There was slight wrist-drop, inability to extend the wrist more than five degrees, partial loss of the power to extend the fingers, and diminution of sensation over the radial and posterior surface of the forearm, although this could not be accurately determined, owing to the fact that the patient spoke nothing but Polish. At the end of eight weeks, treatment by massage, passive motion, and electricity, there was no improvement, either in the sensation or motor power, and operation was accordingly decided on. Exposure of the nerve showed a narrowing at the point of injury to a quarter its normal size. The narrowed portion was excised, the cut ends sutured with fine silk, and the wound closed.

Sensation was apparently as good the next day after the operation as before, but here, again, no accurate information could be gleaned, on account of the patient's inability to understand English. Six months after the accident, the patient was at work with a useful hand, and at the end of a year, function was practically completely restored.

CASE 6. Frank Y., aged 29, rod-roller, first consulted me sixteen months after a compound comminuted fracture of the humerus about its middle. Examination showed complete wrist-drop, with inability to extend the wrist or fingers, either actively or passively; marked atrophy of the muscles of the forearm, especially the extensor group; prominent spaces between the metacarpals; and a glistening, shiny skin, with absence of sensation over the area of musculospiral supply. Operation was advised, and agreed to by the patient. The nerve was isolated at the level of the old fracture, and found to be involved in a mass of cicatricial tissue, above which was a bulbous enlargement of the nerve, while the distal portion was found to be much attenuated. The cicatricial tissue was removed, together with a portion of the bulbous enlargement of the nerve, and the cut ends united in the usual manner.

Sensation began to return at the end of six weeks, and motion at the end of four and a half months. At the end of a year the patient had the power to extend the wrist about forty degrees, and nearly complete power of extension of the fingers, but was unable to lift the fingers in the piano-playing position. At this time, he moved away from the city and was lost sight of, but as the improvement had been steady up to the time of the last observation, there is good reason to hope that time brought a nearly perfect restoration of function.

Do the above clinical records help in any way towards solving the questions propounded at the beginning of this report? In the first place as to the question of diagnosis between contusion and partial and complete severance of the nerve, the symptoms may be identical in both cases, and some writers argue that if, from the nature of the injury, there is doubt as to whether the symptoms are due to simple contusion, operation should be urged immediately, for the following reasons.

The operation, in itself, is usually simple, and if a normal-looking nerve is found, and the operation thus proves to have been unnecessary, no harm has been done. On the other hand, if a severed or crushed nerve is found, the time gained by immediate operation is invaluable, for the longer one delays operation after a nerve injury, the more likely is one to find degenerative changes in the muscles and joints, which seriously interfere with obtaining a good end result. However, patients are not in the habit of welcoming any operative procedure with any degree of joy, and if an operation proves to have been unnecessary, it is certainly distinct evidence of the limitations of our powers of diagnosis, and to some extent a discredit to our profession.

How long shall we wait, then, after traumatic paralysis of the nerve before urging operative interference, and what guides have we in making our decision? This is a question of much importance, and has received many different answers. Henricksen would operate a month after the injury if there has been no improvement, and some others advise even earlier operation; Bowlby would wait three or four months; Sachs, more than three and a half months; and some observers, even twelve to eighteen months. In the writer's first case, three months elapsed before any evidence of motor return was recorded. In Bowlby's case (1), in which operation was done at the end of three months, and a normal-looking nerve found, it was still another month before any motor improvement set in. Hammond (2) mentions a case of a boy with a facial palsy following a mastoid operation, in whom motion in the affected muscle was first noticed fifteen months later. The advocates of early operative interference maintain that if an injury is found that necessitates suture of the nerve, not only has much time been saved by not waiting, but the final results are more likely to be perfect. This, in the main, is true, and with male patients having injuries in which the operation scar would not be conspicuous, it would be legitimate, perhaps, to urge operation on these grounds, but in the first case recorded by the writer, the patient happened to be a beautiful woman, who was in the habit of appearing in the conventional modern evening dress with short sleeves. Would she not have had just cause for resentment if an unnecessary operation had been performed, leaving her with a conspicuous scar as a reminder of the limitation of the surgeon's knowledge?

A very noticeable feature of all these cases is, that sensation always returns weeks before motor power, and I believe that the condition of the sensory recovery gives us valuable assistance in making up our minds when to operate. If in these cases sensation begins to improve in two or three weeks, and goes on to practically complete recovery in one or two months, we should feel justified in waiting four months or more for beginning return of motion, and a year or more for complete recovery. But if the sensory return is poor or is absent, it is evident that we cannot expect much, if any, motor recovery, and in such cases a delay of six or eight weeks before urging operation should be sufficient.

The sensory condition of the part affected then should be watched with extreme care, as it is a great help in telling us what we may expect of motor recovery.

We have yet to consider the questions: How long a time after injury may we promise any results from operative relief? and, How much hope of improvement may we hold out in such cases? Furthermore, how long a time must the patient wait after operation before improvement will begin? and how long a time will elapse before the maximum improvement will be reached?

In cases of primary suture, most surgical observers are agreed that restoration of function does not occur, as a rule, until two months after the primary suture. We may, in general, expect practically a perfect recovery following primary suture in from two months to a year, but it is never best to promise an absolutely perfect functional result.

A large number of cases of secondary suture of nerve has been recorded in which recovery occurred. Sensation always returns weeks before motor power, and motor power months, or even a year, before electrical reaction.

In the writer's cases, sixteen months was the longest time after injury before operation was done, in which case a good functional result was obtained, but the patient passed out of observation before hope of further improvement could be abandoned. The time of beginning sensory return varied from two days to six weeks, and from eight weeks to three months for its complete recovery. The motor recovery began in from eight weeks to six months, and was complete in from six months to over a year. So long ago as 1871, Jessop (3) reported a case where, after the lapse of nine years after the division of the ulnar nerve above the wrist, there was still anæsthesia and paralysis. Secondary suture was performed, with the result that sensation returned after three days, motor power after ten weeks, and restitution after nine months. In Robson's case (4) of ulnar paralysis of two and a half years' duration, sensation is reported to have returned on the third day, motor power in three months, and complete recovery in one year; and in Ogston's case (5) of affection of the same nerve of like duration, sensation began to return in a week. In one of MacCormack's cases (6), after six years' total ulnar paralysis, some return of sensation was reported on the day after the operation. In another of his cases — that of ulnar paralysis of six weeks' duration, the result of a bullet wound — the lacerated part of the nerve was excised and the ends joined by suture; sensation began to return thirteen hours after operation; motor result not reported. Ballance and Stewart (7) report a case of paralysis of the external popliteal nerve following a bullet wound, which showed distinct return of sensation when examined one and a half hours after operation. In Kennedy's four cases (8), sensation commenced to appear on the third or fourth day after operation, and motion in from three weeks to six months, the nerve having been previously paralyzed for a period varying between three and eighteen months. Henricksen (9) reports a very interesting series of nine cases of secondary suture, at periods varying from a month to two and a third years after the injury, with a practically perfect functional result in every case, although motor function in one instance was over two years in reaching a nearly perfect recovery. Numerous other cases of successful secondary nerve suture have been reported in the literature of recent years, most of them successful. A number of cases of failure of motor return have been reported, but the majority of these have been related too soon, in my opinion, to despair of further improvement. With the exception of Jessop's case (3) of nine years' duration, with perfect result, I have been unable to find any case of satisfactory motor return following secondary suture after an interval of two and a third years. Bowlby failed once at twelve years, once at six, and again at four years, to gain any motion worth while by secondary suture, but succeeded invariably under two and a half years.

With primary suture, then, we may be practically sure of a good result. But if the injury is of some standing, we may say that up to one month a practically perfect result may be expected, although not promised the patient; up to two and a half years we may expect a good functional result; beyond that period little can be promised beyond a return of sensation; but in view of an occasional success I believe that we should be justified in urging operation.

We may expect a return of sensation in a time varying from a few hours to several weeks. We may expect little or no motion under three months, and no perfect result much under a year, while we must not despair of improvement under two years.

A very important phase of this subject concerns the treatment of the paralyzed part during the stage before and after operation. Too great emphasis cannot be laid upon the necessity of keeping the nutrition of the affected skin and muscles in the best possible condition by the use of massage, passive motion, and the galvanic current. Patients are prone to consider these measures as unnecessary and a bore, as improvement is so slow to appear and progresses at such a snail's pace, but the systematic use of such treatment makes all the difference between a good and a poor end result.

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SUTURE OF THE SPLEEN FOR TRAUMATIC HÆMORRHAGE.

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(*Surgical Service of Dr. Dudley P. Allen.*)

IN the November number of the ANNALS OF SURGERY, 1904, there appeared an article, by Williams, of Chicago, entitled " Penetrating Wounds of the Chest perforating the Diaphragm and involving the Abdominal Viscera." In this report he states that his case is the only successful one of suture of the spleen for traumatic hæmorrhage reported in this country, except the one of Tiffany, of Baltimore, in 1894.

Two days after performing the operation described below, the above article was first noticed. It seems fitting that this third case should be added to the list, inasmuch as the cases seem to be of such rare occurrence.

The patient, R. W., male, aged twenty-four years, was admitted to Lakeside Hospital, November 11, 1904, with a history of having received two stab-wounds in the left side while engaged in a scuffle with a fellow-workman. The wounds were inflicted with a candy-maker's knife which had two blades set in a heavy handle.

The case was operated upon during the service of Dr. G. W. Crile, Associate Surgeon, and by his permission was intrusted to my care.

Examination on admission, one half-hour after injury:
Mucous membranes, anæmic.
Skin cool, covered with perspiration.
Temperature, 98.3° F.
Pulse, 120; regular, small volume.
Respiration, 30; some dyspnœa.
Head and neck, normal.

Thorax.—Inspection revealed a wound two centimetres in length in the ninth interspace in the left midaxillary line through which protruded a portion of tissue three centimetres in length. This tissue had the appearance of omentum. The skin wound was two centimetres above the intercostal wound (apparently due to the direction of the blow, so that the skin acted as a valve. When the skin was retracted, air would rush into the pleural cavity upon inspiration and be expelled synchronous with expiration. The amount of hæmorrhage from this wound was slight. Percussion revealed a small area of dulness, three centimetres in diameter. A second wound was found in the eleventh interspace directly below the first wound. A tag of omentum six centimetres in length was protruding from this wound, and just below it was an area of distinct dulness. A slow but apparently increasing amount of bright red blood was oozing from this wound.

Heart and lungs, normal.

Abdomen, normal in appearance.

Operation.—Under ether anæsthesia the area about wounds was cleansed and digital examination was made. The upper wound was found to extend into the pleural cavity, but did not apparently involve the lung. Through this wound the diaphragm could be palpated, and it was found to be cut away from its costal attachment for a distance of six centimetres. When a finger was inserted into the lower wound, it met the finger inserted in the upper wound. The tags of tissue were found to be omentum, and, in order to avoid chance of infection from this source, the tags were cut off with plain catgut, and the stump of the upper tag of omentum was returned to the abdominal cavity through the opening in the diaphragm. The lower wound was enlarged downward and forward for a distance of six centimetres, and it was apparent that there was a very active hemorrhage in this region. After sponging out the excess of blood, a portion of what appeared to be a cut spleen was seen. This was seized with a hæmostat and carefully drawn as far as possible to the wound. In one portion of the cut surface a spurting artery was found and clamped.

Further examination proved the organ to be the spleen, which showed a cut four centimetres in length extending almost through its substance somewhat obliquely to the long axis in its upper third. The cut surfaces were brought in apposition by mattress sutures of plain catgut No. 2 on a curved, round needle. This seemed to be sufficient to control the hæmorrhage. The diaphragm was then sewed to its original attachment by interrupted sutures of chromic gut No. 3. A small cigarette drain was inserted in both wounds. The operation was accomplished without resecting a rib. The lower wound was approximated by through-and-through sutures of silkworm gut, leaving simply sufficient room for drainage.

The patient's condition at the end of the operation was fairly good, though the pulse was considerably weaker.

The week following the operation, there was a small amount of discharge of blood and débris from the wound, but no active hæmorrhage. On the seventh day, temperature, pulse, and respirations were normal. At the end of the second week the wound closed. Patient was in a wheel-chair on the nineteenth day and went home on the twenty-third day.

On December 18, two weeks after the patient left the hospital, he wrote saying that he was feeling as strong as usual.

The patient was examined by the writer on March 28, 1905. The scars were very solid, and the general condition apparently excellent. Patient is able to work at his trade (candy-making) regularly, although the work is laborious.

CASE OF
AN
HERMAPHRODITE

BY
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CASE OF AN HERMAPHRODITE.

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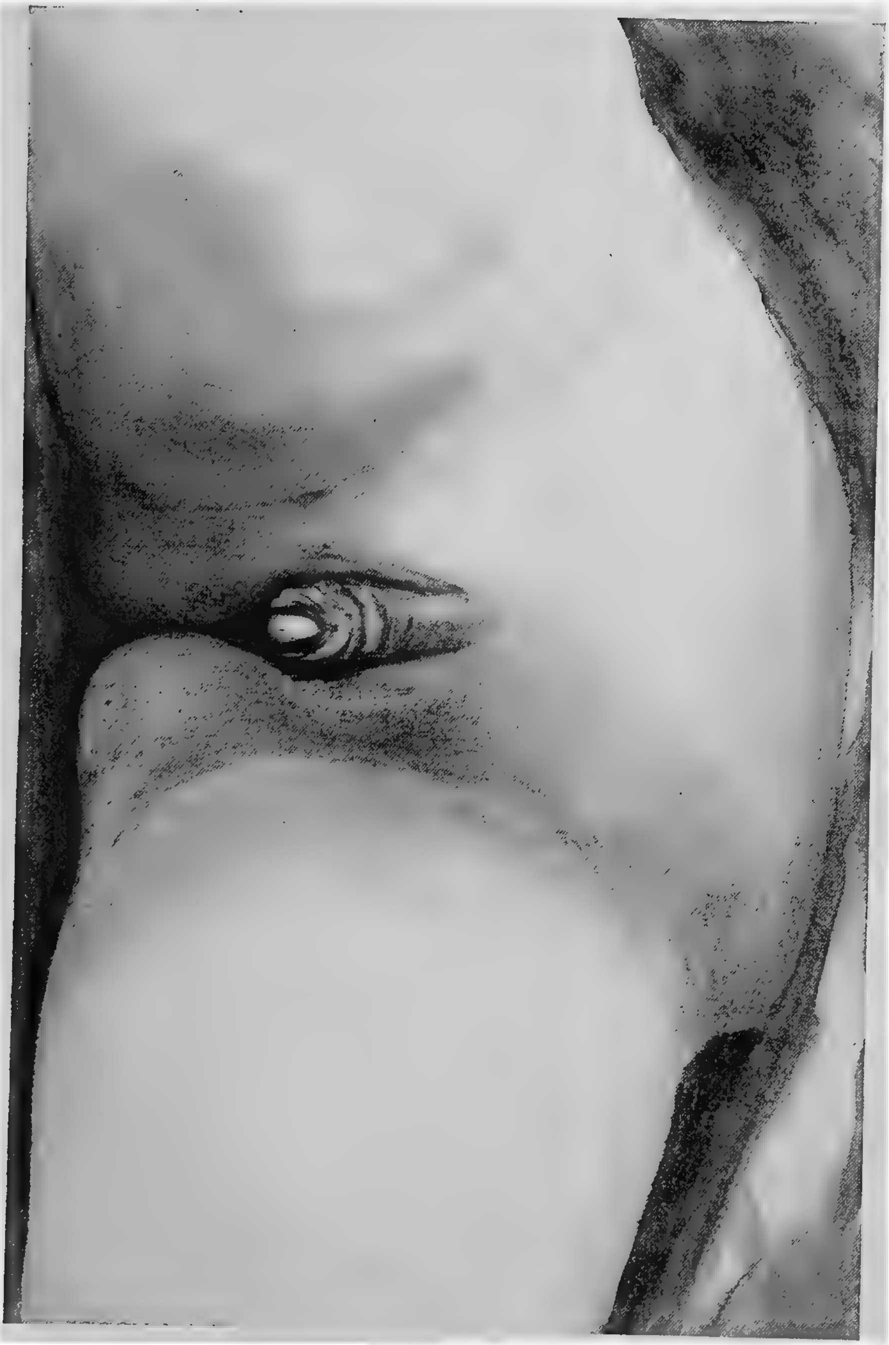
THE accompanying illustration is of an hermaphrodite, aged three years. The parents always supposed that the child was a female. Recently a physician had told them that it was a male. Although the child was still too young to have developed marked characteristics indicative of sex, the face appeared to be that of a girl.

An examination of the genitals showed that the child had an organ which presented every appearance of a penis corresponding to the age of the child. There was a perfectly formed glans penis and a prepuce. The prepuce was, however, adherent to the glans penis a little anterior to its base, and could not be retracted so as to uncover the entire gland. There was an hiatus in the prepuce, along the under surface of the glans, as represented in the accompanying illustration. On attempting to lift the penis from its position, it was found to be adherent along its entire lower surface, a deep sulcus extending along its whole length on either side. On separating the tissues from the sides of the penis, they presented the appearance of the labia majora. On lifting the glans penis, an opening was discovered, and under anæsthesia this was found to be large enough to admit the little finger. This opening extended upward like a normal vagina and had a length of about two inches. On inserting a catheter into the meatus it was found that the meatus was just at the opening of what appeared to be the vagina, but that the orifice of the urethra had less tissue between it and the vagina than normal, it being separated from the vagina anteriorly by a thin septum. The child had entire control of the passage of urine during the day, but was said to wet the bed at times at night.

A nasal speculum was inserted into the vagina, and an attempt was made to gain a view of its upper portion. It was found impossible to make a completely satisfactory examination without overdistending the vagina, so that the effort was aban-



doned. With the little finger in the vagina, a mass corresponding in all respects to the cervix could be felt at the top of the vagina, and on bimanual examination a smaller mass could be felt between the finger in the vagina and the hand above the pubes, corresponding in size and form to the uterus.

The conclusion arrived at was that the child had the reproductive organs of the female, that the clitoris had taken on the over-development of the penis, corresponding to it in all respects, except that it was adherent along its entire under surface to the underlying structures, and that the form of the prepuce corresponded, as shown in the picture, to the covering of the clitoris rather than to the prepuce in the male. What effect erections might have upon the organ could not be determined.

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INFLAMMATORY CONDITIONS OF THE APPENDIX ACCIDENTALLY BROUGHT TO LIGHT IN PELVIC OPERATIONS.*

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THE surgery of the appendix affords one of the most interesting fields which the diagnostician or the operator is called upon to study. In the present paper, however, an attempt has been made to deal not with the broad question of appendicitis, but rather with the lesions that are discovered—one might say almost accidentally—when the abdomen has been opened with the expectation of relieving some morbid pelvic condition, more especially one affecting the tubes and ovaries. In a fairly long series of abdominal operations—some 370—I have made it a routine procedure to examine the appendix vermiformis, and where this organ seemed to be diseased and the condition of the patient seemed to warrant the procedure, I have been in the habit of removing it. In the hope that our experience has not been without value, I shall briefly give the salient points which have been gathered from this series of operations.

In the first place the macroscopical appearances are far from being trustworthy in every case. Thus in quite a number of the instances in which, to us at the time of the operation, the appendix appeared to be diseased, microscopical examination failed to show any signs of inflammatory change. On the other hand, in a measure, the converse is also true. When we find that the appendix, the tubes, and the ovaries are all diseased, the question arises: In which of these structures did the process begin? Not a few operators are of the opinion that an inflammation in or about the appendix can, and not rarely does, spread to the tubes and ovaries. They hold that in many instances a perforation of the appendix takes place and that the accident leads to an inflamma-

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*Read before the American Gynecological Society at Niagara Falls, New York, May 25th, 1905.

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tory involvement of the lateral structures; but that the perforation having healed, the appendix gives no further trouble and at operation looks perfectly normal, while the secondary effects remain. It is hard to believe that such instances are very common, and certainly we are not justified in accepting such a conclusion for any given case unless a microscopical examination has clearly shown that a perforation has at some time taken place. So far as my own experience goes, in over 1,000 abdominal sections for pelvic disorders, I have failed to find positive evidence that in a single case the appendix has been the primary seat of the disease.

In most cases of pelvic peritonitis leading to abscess formation, careful inquiry will elicit a history pointing to an original gonorrhea or to a septic infection following labor or abortion as the starting point of the condition. Again, it is readily seen that an infection which arises from these causes might readily implicate the surrounding structures. This, then, I believe to be the most reasonable explanation in the majority of the pelvic cases in which we find evidence of an old periappendicitis and adhesions. Nor are such conditions rare.

So far as the differential diagnosis between a more or less acute appendicitis and an inflammation of the lateral structures is concerned, the problem, as a rule, is not difficult. If a history of gonorrheal infection or pelvic disturbances following labor or abortion can be elicited, and bimanual examination shows some abnormal enlargement in the region of the adnexa, the morbid condition, or, at least, the predominating lesion, can with safety be decided to exist in the tubes and ovaries.

Whether in all cases in which we find the appendix flexed or firmly bound down by adhesions, we are dealing with a pathological condition which must almost inevitably cause trouble at some future time, is a question that cannot always be answered. It would seem, however, fairly certain that such conditions are not always of special significance. Nevertheless, in these cases I do not see the use of taking any unnecessary chances, and, provided that the patient is in a satisfactory condition, and will not be exposed to any risk by a slight prolongation of the operative procedures, it is my custom to remove the appendix whenever the abdomen is open for other reasons. By adopting this procedure, in the absence of contraindications, I am sure that we have saved many of our patients future trouble, and not a little anxiety.

Of the 370 appendices removed and examined microscopically, 103 were normal, 46 showed signs of a chronic, and 1 of an acute appendicitis. In 88 cases there was a hypertrophy of the subperitoneal or internal coat, or of both coats. In 66 cases the changes were of doubtful significance. In 36 cases the lumen was occluded; in 16 dilated; in 12 contained concretions; in 1 case the appendix was cystic and had undergone myxomatous degeneration; in one case no lymphoid tissue was present.

The following table shows the conditions existing at the time of operation, with the proportion of cases in which inflammatory changes were found in the appendix on microscopical examination:

TABLE.

OTHER CONDITIONS PRESENT.		INFLAMMATORY CHANGES IN APPENDIX.			
Normal tubes and ovaries	136	12	or	8.82	per cent.
Adherent tubes and ovaries	42	2	"	4.76	"
Chronic salpingitis	44	5	"	11.36	"
Tuboovarian abscess	5	0	"	.00	"
Pus tubes	46	7	"	15.22	"
Tubercular salpingitis	8	1	"	12.05	"
Acute salpingitis	3	2	"	66.67	"
Hydrosalpinx	9	1	"	11.11	"
Hematosalpinx	3	1	"	33.33	"
Ectopic gestation	2	0	"	.00	"
Ovarian cyst	9	2	"	22.22	"
Cyst in R. broad ligament (cholesterin)	1	1	"	100.00	"
Parovarian cyst	5	1	"	20.00	"
Mixed conditions	26	8	"	30.77	"
Myomata	10	2	"	20.00	"
Retroversio uteri (adh.)	9	1	"	11.11	"
Descensus uteri (adh.)	7	1	"	14.28	"
Sarcoma uteri	1	0	"	.00	"
R. Perisalpingitis	1	0	"	.00	"
Ventral hernia	3	0	"	.00	"
	370	47		13.46	

PUS CASES.

Pyosalpinx	46	7
Tuboovarian abscess	5	0
Mixed conditions	13	4
	64	11 or 17.19 per cent.

MYOMATA.

Alone	10	2
Mixed conditions	8	1
	18	3 or 16.66 per cent.

A few points of interest may be noted in connection with certain groups in this table. The total number of cases which showed inflammation of the appendix is 47; 12 of these were found in conjunction with a normal tube and ovary, and the morbid condition for which operative procedures were instituted were various—retrodisplacements of the uterus with or without adhesions, resections of graafian follicles, puncture of graafian cysts, etc. In 42 cases adherent tubes and ovaries were met with, and in this group there were 2 cases of inflammation of the appendix. In 64 pus cases in 11 (about 17 per cent.) there was an appendicitis. In 148 cases showing inflammatory conditions affecting the tubes and ovaries; in 25 (16.89 per cent.) there was an appendicitis; in 9 cases of ovarian cystoma there were two cases of appendicitis; in 5 cases of parovarian cyst 1 case of appendicitis; 1 case of cyst (cholesterin) of the right broad ligament showed also an appendicitis. Thus in 15 cases of cystic growths, appendicitis was also present in 4 (26.66 per cent.). It is also interesting to note that in 18 cases in which the uterus was removed for myoma, the appendix showed inflammatory changes only in 3 cases (16.66 per cent.).

Deaths.—In making up such an analysis it is of interest to determine, if possible, whether or not the removal of the appendix could in any way have been concerned in causing the fatal result. In this particular analysis, at any rate, we can fairly assume that the removal of the appendix played no part in producing the deaths. We had four deaths in 370 cases, or a mortality of a little over 1 per cent. for the total number of cases.

CASE I.—Both tubes, and ovaries, and uterus were removed on account of a myomatous tumor, with a right hydrosalpinx and an adherent ovary, also a left chronic salpingitis with an adherent ovary and occluded appendix. The patient died on the fifth day from a septic peritonitis.

CASE II.—Removal of a cyst of the broad ligament, which was adherent to the intestines, tubes and ovaries. The appendix showed chronic inflammatory changes.[1] The patient was in good condition until the fourth day, when pain from distention was treated by a turpentine enema, which was later found in the peritoneal cavity. In all probability the bowel had unwittingly been torn during the separation of the adhesions.

CASE III.—An adherent right ectopic gestation with adherent left tube and ovary, and hypertrophy of the coats of the appendix. Double salpingo-oophorectomy. The patient developed an ileus on the eleventh day due to adhesions. The abdomen was reopened. The patient died from shock two hours following the operation.

CASE IV.—Removal of adherent left tube and ovary, with separation of adhesions binding down the uterus. Death on the seventh day as the result of a streptococcus peritonitis. The appendix showed chronic inflammatory changes.

CONCLUSIONS.

1. In a large number—in our series in 323 out of 370—of pelvic cases no inflammatory changes in the appendix are found even microscopically.

2. When we find a normal appendix in conjunction with disease of the pelvic organs, it is improbable that the latter condition has been brought about by a perforation of the appendix which had afterwards healed.

3. On the other hand, an old periappendicitis and adhesions may often be looked upon as the result of a septic infection, originating in and spreading from the organs of generation.

4. An appendix which looks abnormal macroscopically does not always show inflammatory changes on microscopical examination.

Nevertheless, (5) when the removal of the appendix adds very little to the gravity of the abdominal operation, for the benefit of the patient, it should be taken away.

6. In our our series of 370 cases there were 4 deaths, but a careful analysis goes to show that the fatality could in no instance be attributed to the removal of the appendix.

702 ROSE BUILDING.

Reprinted from the Transactions of the American Gynecological Society, 1906

THE IMMEDIATE RESULTS OF CONSERVATIVE OPERATIVE MEASURES ON THE TUBES AND OVARIES.

By Hunter Robb, M.D.,
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In 1904, I read a paper before the Ohio State Medical Society, in which I presented an analysis of 237 patients upon whom conservative measures had been carried out when dealing with inflammatory lesions of the tubes and ovaries. Since then we have had 182 additional cases, making in all 419 instances in which we have carried out such procedures during the past seven years. We have not included the cases of so-called cystic or cirrhotic ovaries, unless they have been bound down by marked adhesions. We believe that such ovaries are still capable of performing their functions, and the symptoms are apt to be due not to pathological conditions in the ovaries themselves but mainly to adhesions which are binding them down.

But even when the ovaries have undergone actual inflammatory changes, or where they are occupied by tumor formations, or are bound down by adhesions so that their functions are interfered with, and the necessity of operative procedures becomes imperative, we still have to decide how far we ought to go and how we can get the best results for the patient not only immediately but later on. From our experience in this line of work for more than seven years we have been able to thoroughly convince ourselves of the great advantages that may be obtained by preserving as far as possible the integrity of the pelvic organs. It is true that in a small percentage of cases (2 to 5 per cent.), after such a line of treatment has been followed, the patient will still have to undergo a second operation before she can be completely relieved of her discomfort, and it is also possible that in a few instances, by the introduction of infection under these circumstances, her condition may be rendered even worse. Such cases, however, in our experience are exceptional. Moreover, a secondary operation is not infrequently necessary in cases where radical measures have been carried out, hence it is not altogether fair to blame the conservative measures for the second operation. We all have had the experience (in a small percentage of cases) of separating post-operative adhesions after carrying out radical measures. Before, however, employing the more conservative procedures we always make it the rule to carefully explain to the patient, or to her friends, that such measures will be undertaken if, in our judgment at the time of the operation, they seem to be advisable. But we further state that, even though we remove what seems to be the inflammatory area, it may later become necessary to institute a secondary operation before relief is obtained. After this very clear statement has been made to the patient, as a rule she is perfectly willing to take a good many chances if there is a reasonable prospect that the conservation of the pelvic organs will be compatible with future health and comfort, and, as we have already said, from actual observation we have found that it does not become necessary to perform a secondary operation in more than from 2 to 5 per cent. of all such cases. If an ovary or a portion of an ovary can be saved before the menopause has begun, or even during the time in which the patient is experiencing this change, we have found that not only the immediate convalescence, but also the subsequent condition of the patient, is in every way more satisfactory. I am sure that all of us have seen many patients suffer more after than before the removal of diseased ovaries. In many instances their discomfort is due to the artificial change of life that is thus brought about. In some instances they may complain for five years or longer. And, unfortunately, during this time the addiction to morphine or some other drug habit may be formed in endeavors to relieve their distress. In our opinion the prevention of the artificial menopause is the most important reason for leaving the patient her ovaries whenever this is possible, the question of possible pregnancy following conservative measures being apparently only of secondary importance, as in the majority of these cases the patient is in an unhealthy condition not only for bringing a child into the world, but also for the proper rearing of the same. This criticism, of course, does not usually apply to those cases in which a tumor is present, implicating only one ovary. Where the question of pregnancy is to be considered one has to deal with the condition of the Fallopian tubes as well as that of the ovaries. I will not take up your time with an account of the various methods that are employed in carrying out the conservative measures, as they are perfectly well known to every one. I would say, however, that in the light of our experience it is a wiser procedure to remove the Fallopian tube whenever a pyosalpinx exists, *i. e.*, when there are macroscopic evidences of pus. When, however, the ovary is involved in an abscess formation the same radical treatment is not always indicated, as the abscess in most instances does not involve all of the ovarian stroma. Furthermore, microscopic examination of many of these ovaries will show that the abscess is walled off and the ovarian stroma beneath frequently has been invaded only to a slight extent. In such instances the abscess may be excised and the line of incision be brough together with a fine silk or catgut suture. In our series of cases the lateral structures showed macroscopically marked evidences of inflammatory disease, and there were adhesions which bound down the structures. We have only included in this analysis those cases in which we were able to carry out conservative measures, and not those in which we were obliged on account of the technical difficulties of the operation to leave the lateral structures in, on one or both sides, although removal was indicated.

ANALYSIS OF CASES.

Total number, 419. Age: The oldest patient was fifty-two years of age; the youngest, fifteen years of age. Average age, 28.98 years. 1 was fifteen; 1 was sixteen; 9 were seventeen; 14 were eighteen; 18 were nineteen; 14 were twenty; 19 were twenty-one; 24 were twenty-two; 21 were twenty-three; 24 were twenty-four; 22 were twenty-five; 18 were twenty-six; 14 were twenty-seven; 28 were twenty-eight; 17 were twenty-nine; 26 were thirty; 11 were thirty-one; 14 were thirty-two; 15 were thirty-three; 7 were thirty-four ; 16 were thirty-five; 12 were thirty-six; 5 were thirty-seven; 17 were thirty-eight; 10 were thirty-nine; 9 were forty; 4 were forty-one; 6 were forty-two; 2 were forty-three; 3 were forty-four; 5 were forty-five; 3 were forty-six; 4 were forty-seven; 3 were forty-eight; 1 was forty-nine; 1 was fifty; 1 was fifty-two. The majority of the patients were between fifteen and twenty-eight years of age.

Menstrual History. The menstrual history was abnormal in 290 and normal in 129 cases.

Leucorrhea. 321 patients gave a history of a leucorrheal discharge. Of these 233 were married, 65 were single, and 23 widowed.

Married Life. 300 were married; 85 were single; 34 were widows. Longest time married, thirty years; shortest time married, two months. Of the 300 married, 207 had borne children. The total number of children borne by the 207 were 502, the average being 1.67 children to each married woman. The greatest number of children borne by one patient was 12. The next greatest number was 11. Stillborn children, 6. Twins 1. Women having borne one child, 98; two children, 43; three children, 32; four children, 24; five children, 8; six children, 7; seven children, 5;

eight children, 1; nine children 2; eleven children, 1; twelve children, 1.

A history of infection following labor was recorded in 55 cases. Instrumental delivery was followed by infection in 18 cases. The total number in which there was a history of infection following labor, 73.

Miscarriages. Number of patients having had miscarriages, 177; number of miscarriages, 304; married, 146; single, 14; widowed, 17. Abortions or miscarriages had been induced in 81 cases; in the married patients, 53; in single patients, 18; in widows, 10; patients having had one miscarriage, 107; two miscarriages, 42; three miscarriages, 19; four miscarriages, 2; five miscarriages, 4; six miscarriages, 1; seven miscarriages, 1; fifteen to twenty miscarriages, 1.

Gonorrheal Infection. In 102 patients there was a history of gonorrheal infection; positive in 72; probable in 30. Of these, 60 were married, 33 single, and 9 widowed.

Among the married the history was positive in 39, probable in 21, and in 1 was complicated with syphilis.

Among the single the history was positive in 27 cases, probable in 6, and in 1 was complicated with syphilis. Among the widows, positive in 6, and probable in 3.

A positive history of a specific infection is generally difficult to obtain, and unless the infection can be surely proved, we are not justified in making positive deductions from this standpoint. It will be seen from a study of the cases of labors and miscarriages that infection in these instances plays a very important part in the causation of inflammatory diseases of the tubes and ovaries. Thus, there were 73 cases of infection following labor and 51 following miscarriage—in all 124 cases.

Bowels. In 189 cases there was a history of constipation. 132 of the patients were married, 34 were single, 23 widowed.

Micturition. There was some complaint with this function in 214 cases. 157 of the patients being married, 38 single, 19 widowed.

The general condition was good in 233 cases; in 159 fair; and poor in 27.

The uterus was adherent in 195 cases. 138 of the patients were married, 48 single, 9 widowed.

The bowels were adherent in 223 cases. 150 of the patients were married, 56 were single, 17 were widowed.

The vermiform appendix was removed in 218 cases· Married, 158; single, 44; widows, 21; In 89 married patients it was adherent; in 22 flexed; in 3 occluded; in 16 hypertrophied. Single: 33 adherent; 8 flexed; 2 occluded; 4 hypertrophied. Widows: 18 adherent; 3 flexed; 3 occluded; 2 hypertrophied.

It was adherent and not removed in two cases on account of an extreme condition of shock after removal of the pelvic structures, and in three cases it was not located readily, and on account of condition of patients it was not deemed advisable to make further search. 2 patients were married, 3 single.

	Cases.
The appendix was adherent in	140
The appendix was flexed in	33
The appendix was occluded in	8
The appendix was hypertrophied in	22
The appendix was dilated in	7
The appendix had concretions in	8

Structures Saved

Ovaries:

	Cases.
Right	134
Left	127
Both (80 times)	160
Right (partial)	39
Left (partial)	28
Both (partial in 10 cases)	20
Both ovaries with tubes (32 times)	64
	572

This number (572 ovaries) were saved in 419 cases; 1.34 ovaries to each patient.

Tubes

	Cases.
Right	32
Left	42
Both (37 times)	74
Right (partial)	19
Left (partial)	13
Both (partial) (17 times)	34
Total	214

In 419 cases, or a little more than half a tube to each patient.

Structures Saved in the Pus Cases.

Pus was met with in 97 cases out of the 419, or in 23.17 per cent.

They were divided as follows:

	Cases.
Married	60
Single	30
Widows	7
	97

The pus as follows:

Double pyosalpinx:

	Cases.
Married	34
Single	9
Widows	4
	47

Single pyosalpinx:

	Cases.
Married	12
Single	7
Widows	1
	20

Tubo-ovarian abscess with pyosalpinx (single):

	Cases.
Married	10
Single	3
Widows	0
	13

Tubo-ovarian abscess (double):

	Cases.
Married	1
Single	8
Widows	0
	9

Tubo-ovarian abscess (single):

	Cases.
Married	2
Single	2
Widows	1
	5

Tuberculous ovarian abscess:

	Cases.
Married	1
Single	0
Widows	0
	1

Ovarian abscess (double):

	Cases.
Married	0
Single	1
Widows	1
	2

Structures Saved in Pus Cases.

Ovaries.	Cases.	*Tubes.*	Cases.
Right	32	Right	7
Left	30	Left	3
Both (16 times)	32	Right (partial)	2
Right (partial)	7	Left (partial)	4
Left (partial)	3		16
	104		

Thus 104 ovaries were saved in 97 pus cases, or about 1.08 ovaries to each patient. In 16 cases both ovaries were saved. 16 tubes were saved, or 1 to every six and a half patients. In these cases the following organisms were found:

	Times.
Gonococcus	10
Streptococcus pyogenes (1 doubtful)	4
Staphy. pyog. aureus	6
Staphy. pyog. albus	2
B. coli communis	4
B. mucosus capsulatus	1
Cocci in smears (no growths)	6
	33

In all, or one-third of the cases.

In the pus cases the abdominal wound became infected seven times, or 7.53 per cent. From the infected abdominal wounds in the pus cases the following micro-organisms were isolated:

	Times.
Streptococci	1
B. coli communis	2
Staph. pyog. aureus	3
Staph. pyog. albus	1
B. mucosus capsulatus	1
	8

Micro-organisms found in abdominal wounds other than pus cases:

	Times.
B. coli communis	4
Staph. pyog. aureus	1
Staph. pyog. albus	3
Cocci and bacilli on coverslip; no growth	2
	10

The leukocyte count in the pus cases:

Highest	36,000
Lowest	3,400
Average count	17,597

Drainage was employed in the pus cases as follows:

	Times.
Abdominal alone	0
Vaginal	24
Abdomino-vaginal	4

28 times, or in 29.17 per cent. of all pus cases.

Drainage was carried out 42 times in 419 cases, or in about 10.24 per cent. of the total number of cases. Once by the abdomen alone; 5 times by the abdomen and vagina combined; 36 times by the vagina alone.

The convalescence was interrupted by the following conditions: Bronchitis in 4 cases; pneumonia in 2; pleurisy in 6; phlebitis in left leg in 1; phlebitis in left arm in 1; diarrhea in 2; stomatitis in 4; peritonitis in 2; paralysis of left arm in 2; paralysis of right arm in 1; intestinal obstruction in 1; acute gastritis in 1; perirectal abscess in 1; tonsillitis in 1;

angina in 1; abortion in 1; rheumatism in 2; dyspnœa in 1; fistulæ—abdominal fecal and urinary in 1; abdomino-vaginal (fecal) in 1; rectovaginal in 1; abdominal in 1; abdominal (fecal) in 2; suppuration of abdominal wound in 37 cases. Total number interrupted, 79.

In those cases interrupted by infection of the abdominal wound (15 of which were in the pus cases), 19 of the infections were slight and two marked. Total number of abdominal wounds infected 8.56 per cent. *Number of cases requiring a secondary abdominal operation for the relief of symptoms,* 10. *Number of cases under observation on account of pelvic discomfort,* 13. *In* 10 *of these cases the symptoms of which the patient complained disappeared after one year. Three are still complaining.*

Deaths in the pus cases were 3 (or 3.04 per cent.).

Deaths in the whole number of cases (419) were 7 (or 1.67 per cent.).

Among the pus cases the diplococcus pneumoniæ was found in the secretions in the peritoneal cavity in one, together with B. mucosus capsulatus and B. coli communis.

Another patient died from the effects of a pelvic peritonitis; autopsy not allowed.

In one case there were extensive adhesions which were separated about the lateral masses and between the bowels and masses. On the ninth day after the operation the bowels could not be moved by either purgatives or enemata. On the thirteenth day the abdominal cavity was opened to find the cause of the obstruction. The small intestines were found adherent to each other. These adhesions were separated but the condition was not relieved, and the patient died the fourth day after reopening the cavity.

The four remaining cases were in the non-suppurating class.

In one there was an ectopic gestation which had involved the right tube. On the eleventh day following the operation she developed an acute obstruction of the bowels. The temperature and pulse were practically normal. The abdomen was reopened and the obstruction relieved, but she succumbed from shock one hour following the operation. In the second case the disease of the lateral structures was complicated by an adherent, much thickened, and contracted gall-bladder, which contained three good-sized gallstones. The opening made into the gall-bladder was difficult to close. The patient developed a localized peritonitis, which resulted fatally five days after the operation.

In the third case the pulse and temperature both began to fall after operation. The patient roused slightly, then gradually sank into a comatose state and died early the next morning.

In the fourth case a plastic operation was done, and on the fourteenth day an abdominal section was done. On the eleventh day after, patient died. For three days before death temperature and pulse gradually rose, but nothing was made out on examination to account for the condition.

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PULMONARY COMPLICATIONS FOLLOWING ABDOMINAL OPERATIONS

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IN order to obtain some idea of the frequency with which an inflammatory condition of the lungs may follow abdominal operations, we have made an analysis of 1007 consecutive abdominal sections that have come under our observation during the past seven years. Formerly, and to some extent to-day, one hears the term "ether pneumonia" employed in explanation of the fatal result that has followed an abdominal operation. That a pneumonia may result indirectly from the irritating effects of this drug, there can be no question, but recent observations at the autopsy-table go to prove that in the great majority of these cases the pulmonary complication has been due to the extension of a septic process which has originated from the field of the operation. This term undoubtedly, therefore, like heart failure, shock, uræmia, obstruction of the bowels, etc., is often employed incorrectly.

We will here consider quite briefly some of the factors which are undoubtedly concerned in producing these lung complications, and offer certain suggestions that experience would seem to teach are of value in preventing the occurrence of such sequelæ.

The Anæsthetizer.[1] There is a considerable difference at times in the methods employed in the giving of an anæsthetic. The better the anæsthetizer, the less will be the amount of ether used. Until a physician has had an abundant experience in this work, the patients are more likely to develop some lung involvement. In a hospital service it is a difficult matter to allot this duty to one man for more than from four to six months. To some extent it is possible to overcome this drawback by training each new man by first allowing him merely to assist with the giving of the anæsthetic to a dozen or more patients, and until he becomes more proficient, the operator should keep under his observation the administration of the anæsthetic. Particular care should always be taken not to allow the patient to inspire any vomited material.

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[1] Eight of the 35 cases that presented complications following the anæsthetic occurred in the early experience of the anæsthetists. There were 7 cases in the fourth, 6 in the fifth, 5 in the sixth, 4 in the third, and 5 in the second month's experience. The total number of anæsthetists was 16, or 61¼ patients to each anæsthetist. The greatest number developing complications for one anæsthetist (six months' service) was 6 cases, and for another, 5 cases.

The Anæsthetic. The method now commonly employed of producing a primary narcosis by the use of nitrous oxide gas, and then following it with ether, has proved very satisfactory in the great majority of cases. Moreover, the ether must be free from any impurities, as it has been shown that an adulterated brand has frequently caused an inflammatory involvement of the respiratory organs. If the patient secretes a considerable amount of mucus from the posterior nares and the mouth during the administration of the anæsthetic, this inconvenience can frequently be overcome by a hypodermic injection of atropine sulphate 0.75 grain.

The Duration of the Anæsthesia. As a general rule, it may be said that the quicker the operation is performed, the less will be the amount of shock experienced by the patient. On the other hand, carefulness and thoroughness in our manipulations should never be sacrificed to speed. It will very often happen that much better work can be carried out by keeping the patient under the anæsthetic for an additional ten minutes or more, and it is in the exceptional case only that this increased length of time will be productive of any harm.

The General Condition of the Patient. Frequently, patients are operated upon without having been subjected to a careful physical examination. It is a better routine (unless the operation is for an emergency) to keep the patient under observation for two to four days, at least, before she undergoes a serious operation. By observing such a routine, any abnormality of the lungs or other organs that may be present can hardly fail to be detected. During this time of observation, every possible means should be carried out to bring the patient into as good a general condition as possible, in order that she may go through the shock of the operation.

The Temperature of the Operating-room. The temperature of the operating-room should not be below 80° F. During the winter months it is better to maintain the temperature of the room at 85° F. or 90° F. If the operating-room is sufficiently warm, the operator can wear light-weight underclothing and the ordinary operating-room suit with comfort. Under such circumstances, if the patient is properly protected, the room will usually be warm enough. If the ordinary hot-water, hot-air, or steam-heating appliances do not produce a sufficient degree of warmth in the room, a gas-stove should be in readiness for temporarily heating the room.

The Care of the Patient during and Immediately Following the Operation. During the winter, spring, and autumn months, before the patient is taken from the ward to the operating-room, the entire chest should be enveloped with a "pneumonia-jacket." As soon as the patient is anæsthetized and placed upon the operating-table, a blanket is placed over the portion of the jacket that covers the anterior chest-wall. The hips and thighs are also enveloped in a blanket. The buttocks and trunk rest upon thick pieces of muslin, which are in contact with the glass top of the table. As soon as the abdomen has been cleansed, a thickly padded compress is placed under the back and the hips. By carrying out this detail we have never found it necessary to employ the hot-water pads that are used by some operators. The usual protecting towels and sheet are now placed in position.

The abdominal viscera should be exposed and handled as little as possible, and in order to prevent this taking place, as soon as the abdomen is opened we place a good-sized dry gauze sponge, or one wrung out of hot saline solution, against the intestines in the upper abdominal zone. This sponge also prevents the intestines from coming in contact with the field of operation. Just as soon as the operative procedures are finished, we irrigate the pelvis with one or two liters of a normal solution, at a temperature of 112° F. After sponging out this fluid, we introduce from 500 to 1,000 c.c. of a warm normal saline solution into the abdominal cavity, and allow it to remain there. After the abdomen is closed and the dressings have been applied, the patient is given a stimulating enema, consisting of a pint of a warm salt solution, with two ounces of brandy, twenty grains of the carbonate of ammonium, and one twentieth of a grain of the sulphate of strychnine. If the "pneumonia-jacket" becomes soiled or wet during the operation, the chest is wiped dry, and another jacket is put on before the patient is taken from the operating-room. The use of the jacket and the stimulating enema we consider of great value as prophylactic, in preventing the development of shock and pneumonia following an abdominal operation, since, in spite of all possible precautions, the patient is sometimes subjected to a considerable amount of exposure immediately following the operation, before she is placed in her bed. Again, the jacket is of value if the patient should become exposed to a draught while unconscious, and especially during the night-time, when she cannot, as a rule, be so well taken care of. It is also important, during the continuation of the anæsthesia, to guard against the inspiration of any vomited material, which would be apt to produce an "inspiration pneumonia." To prevent this, the patient should be constantly looked after, and all such material should be carefully removed from the mouth.

ANALYSIS OF CASES

In 1007 abdominal operations, 35 (3.5 per cent) of the patients developed a post-operative inflammatory lesion of the respiratory tract (bronchitis, pneumonia, etc.). There were 3 cases in 1898, 7 in 1899, 10 in 1900, none in 1901, 2 in 1902, 4 in 1903, 5 in 1904, 3 in 1905, and 1 in 1906 (to June 20th).

The Months of Greatest Frequency. As one would naturally expect, the greatest number of cases occurred during the winter months, as shown by the accompanying chart. It will also be seen that during the month of July there is an elevation of this percentage column. This fact may be explained by the occurrence of the damp days so common during the early part of this month. It is possible, also, that the patients are not so well protected against the exposure to draughts, etc., as they are in the colder months.

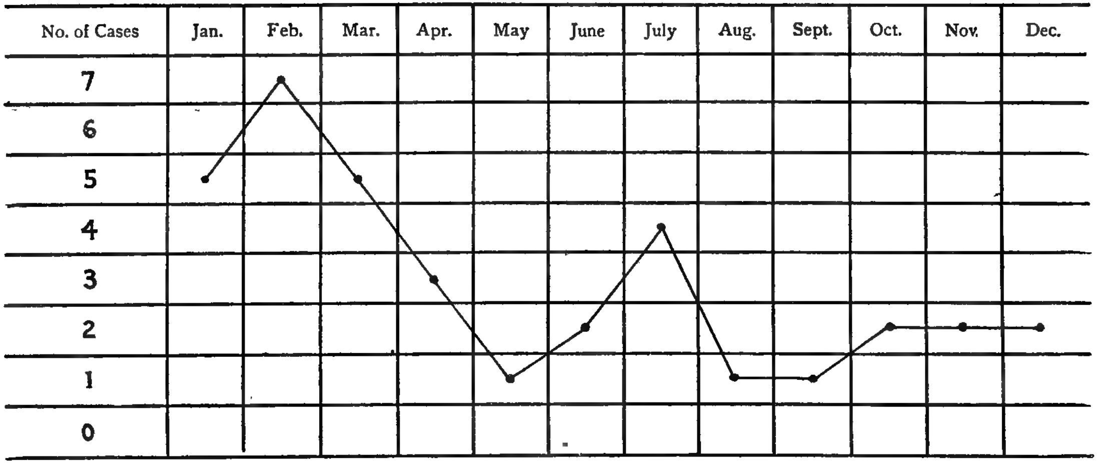
Age. The oldest patient was 49 years old; the youngest, 17. The average age was 32. In this particular series the aged did not show a greater susceptibility to lung complications than did the young. The greatest frequency took place in the third decade, 14 cases being recorded. This incidence may have been influenced by the fact that the greatest number of operations took place in this decade, and also that most of the operations were possibly of a serious nature.

Physical Condition. In 31 cases the examination of the chest gave negative results prior to the taking of the anæsthetic. In one patient who had a cough, but in whom the physical signs in the chest were negative, following the operation, a diffuse bronchitis developed. In another patient with a narrow, phthisical chest, the physical signs were negative. Following the operation, râles could be made out over the entire chest, and tubercle bacilli were also present in the sputum. In a third patient, numerous crackling râles were heard in the axillæ, and over the right lung the percussion note was of a higher tone than normal. An exploratory cœliotomy was performed of cancer of both of the ovaries, with extensive abdominal metastases. The patient did well until the fifth day, when a bronchopneumonia developed, and later proved fatal. In a fourth patient there was some slight impairment of the percussion note over the greater portion of the right chest; the breath-sounds were roughened, and there was an increased tactile fremitus. No râles could be detected. Following the operation, an acute pneumonia developed, which slowly disappeared. This was thought to be due to a tuberculosis, but no tubercle bacilli were found in the sputum, even after repeated examinations.

In a few instances certain unimportant physical signs were made out, which remained unchanged after the operation. These cases, however, are not included in this series.

Personal and Family History. In five instances there

(CHART)


No. of Cases
7
6
5
4
3
2
1
0
Jan.
Feb.
Mar.
Apr.
May
June
July
Aug.
Sept.
Oct.
Nov.
Dec.

was a history of a tuberculosis in the family. In five there had been some previous inflammation of the lungs. One patient was addicted to the cigarette habit.

Anæsthetics. Squibb's sulphuric ether is the anæsthetic generally used in our clinic. It is usually preceded by the nitrous oxide gas. The average amount of ether used was 372 grams; the greatest quantity in any one case, 700 grams; the smallest quantity, 200 grams.

Length of Time of Anæsthesia. The average length (from the beginning of the time of starting the anæsthetic) of the anæsthesia was 1 hour and 52 minutes; the longest period, 3 hours and 25 minutes; the shortest time, 40 minutes.

Duration of the Operation. The average duration of the operation was 1 hour and 32 minutes; the longest period, 3 hours and 25 minutes; the shortest, 20 minutes.

DIAGNOSES

In this series (of 35 cases) the following conditions were met with:

Vulvovaginitis	1
Relaxed vaginal outlet	5
Endometritis	10
Retrodisplacements of the uterus	11
Myoma uteri	2
Sarcoma uteri	1
Follicular hypertrophy of ovary	9
Flexure of appendix	3
Concretions in appendix	1
Perityphlitis	1
Chronic appendicitis	1
Tubo-ovarian abscess	3
Carcinoma of ovary with metastases	1
Fibroma of ovary	1
Salpingo-oöphoritis	16
Hydrosalpinx	3
Hæmatosalpinx	1
Tubal pregnancy	1
Appendix, Abscess of	1
Pelvic peritonitis, Chronic	7
Ventral hernia	1

Pus. In 8 instances (23 per cent) pus was encountered in the pelvis. In two additional cases an acute purulent peritonitis developed after the operation. In these two instances, a pleurisy with an effusion developed. From one, streptococcus pyogenes was isolated from the fluid from each pleural cavity, and also from the peritoneal cavity. In the second case, staphylococcus pyogenes aureus was found in the fluid from the peritoneal cavity. In all, therefore, in 10, or about 29 per cent, of the cases, pus was present in the pelvis. In the eight original pus cases we were able to demonstrate micro-organisms only once, namely, in a tubo-ovarian abscess, as the result of a streptococcus infection.

OPERATIONS

In 15 cases the operation consisted of both a vaginal and an abdominal procedure. In three cases drainage through the cul-de-sac was carried out.

The following operations were performed:

Dilatation and curettage	12
Anterior colporrhaphy	1
Perineorrhaphy	3
Vaginal puncture	3
Herniotomy (ventral)	1
Exploratory cœliotomy (inoperable carcinoma)	1
Suspension of uterus[1]	12
Myomectomy	1
Supravaginal hysteromyomectomy	3
Separation of adhesions	5
Bilateral salpingectomy	2
Unilateral salpingectomy	1
Ignipuncture of the ovary	3
Bilateral salpingectomy with unilateral oöphorectomy	6
Unilateral salpingo-oöphorectomy	4
Bilateral salpingo-oöphorectomy	14
Appendicectomy	17
Total number of operations	92
Number of cases upon whom a single operation was performed	1
Number of multiple operations	34

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[1] In two of the twelve cases, a suspension operation alone was performed. In the remaining cases, other procedures were carried out at the same time.

PERIOD OF TIME ELAPSING AFTER OPERATION BEFORE APPEARANCE OF LUNG INVOLVEMENT

	No. of Cases
Immediately after operation	9
Second day after operation	12
Third day after operation	4
Fourth day after operation	2
Fifth day after operation	2
Sixth day after operation	1
Seventh day after operation	1
Sixteenth day after operation	1
Seventeenth day after operation	1
Twenty-first day after operation	1

Duration of the Lung Lesion. In three instances the lung complication was terminal in character, and was present for 2, 10, and 36 hours respectively before death ensued. In three cases there were evidences of physical signs in the lungs when the patient left the hospital; one on the thirty-first, another on the seventy-sixth, and a third on the seventy-eighth day following the operation. In the first instance the signs were due to a pulmonary tuberculosis; in the second, to metastases in the lungs from a sarcomatous uterus; in the third, to a thickened pleura. This last patient was operated upon six months later for an empyæma of the right pleural cavity. In the remaining instances the lesions disappeared at the end of the following periods:

3 days in 4 cases.
5 days in 1 case.
6 days in 2 cases.
7 days in 6 cases.
10 days in 2 cases.
14 days in 3 cases.
19 days in 1 case.
20 days in 1 case.

The following were the symptoms of the lung complication, arranged according to their frequency:

Cough in	20
Dyspnœa	11
Pain in chest	10
Fever in	6
Cheyne-Stokes respiration in	1
Bloody expectoration in	1
Chills in	1
Cyanosis in	4
Sharp pain in breathing in	2

Rapid or failing pulse in	2
Restlessness in	1
Aphonia in	1

LUNG DIAGNOSIS

Bronchitis. Of the 35 cases, 18 were due to a bronchitis, 5 being of a very mild nature. One was possibly tuberculous in origin, as there were râles over a localized area in either lung, with a bloody expectoration, although no tubercle bacilli were demonstrable in the sputum. The physical signs present were coarse, moist râles throughout both lungs.

In some of the milder cases, râles were demonstrable only over the bases of the lungs. These patients recovered completely in from 3 to 20 days following the onset of the bronchitis. In one instance there developed a bronchitis following a suspension of the uterus, and a bronchopneumonia occurred three years later, after the removal of an ovarian cyst.

Pleurisy occurred in 9 patients. In 4 cases there was a friction rub with a few râles, but there were no evidences of any fluid in the pleural cavity. In two additional cases fluid could be made out in the pleural cavity. In one of these cases the fluid gradually became absorbed. We believe that the pleurisy in both instances was secondary to the peritoneal infection. All of the above instances of pleurisy recovered.

There were three additional instances of pleurisy, which proved fatal. In one there was an effusion with a sarcomatous involvement of the lungs, which was secondary to a similar condition in the uterus. The involvement of the pleural cavity developed immediately after the abdominal operation, and lasted for 77 days. The metastatic involvement in the lungs was proven by autopsy. In the remaining (two) fatal cases the pleurisy was a terminal infection. In one instance pus was found in both pleural cavities, and in the other the exudate was of a serofibrinous character.

Acute pulmonary tuberculosis developed in three instances immediately after operation. In two, tubercle bacilli were demonstrated in the sputum after the operation. Before the operation the examination of the chest had given negative results.

In a third case the physical signs in the right lung were suggestive of a tuberculous involvement. After the operation an acute tuberculous pneumonia developed, although we were unable to demonstrate any tubercle bacilli in the sputum. These patients had improved when they were discharged from the hospital.

Bronchopneumonia occurred in 3 patients, who recovered, and in 2 in whom the condition proved to be a terminal infection. A sixth case also proved fatal from cardiac dilatation.

Convalescence. In 18 cases the recovery from the lung complication took place speedily; in 2 it was prolonged. In 2 instances there was a severe laryngitis. In 1 there was persistent vomiting for several days. In 1 there was a left femoral phlebitis. In 2 there was a septic peritonitis, in 1 of which there was an abscess of the chest-wall.

Mortality and Analysis of Fatal Cases. There were 5 deaths, or a mortality of 14 per cent for the cases that developed lung complications. Three deaths were from a bronchopneumonia, one from a serohemorrhagic fibrinous pleurisy, together with a streptococcus peritonitis, and one from a pleural effusion, from a malignant disease, which lasted for 77 days after the operation.

ANALYSIS OF FATAL CASES

CASE 1. (Gyn. No. 271.) Exploratory cœliotomy for carcinoma of both ovaries. The growths could not be removed. The patient's condition was satisfactory until the fifth day after the operation, when a *bronchopneumonia* developed, from which she died 36 hours later. The autopsy showed an adenocarcinoma of both ovaries with metastases in the pelvis. There were also present a chronic parenchymatous nephritis and a *bronchopneumonia*.

CASE 2. (Gyn. No. 378.) The patient was operated upon for a right tubo-ovarian abscess. She died on the evening of the fifth day, of a pelvic peritonitis. During the last ten hours of life, the lungs began to fill with mucus. At the autopsy the following findings were recorded: 'Pelvic abscess, fibrinopurulent peritonitis, serohemorrhagic-fibrinous pleurisy, serous pericarditis, congestion and atelectasis of lungs. Streptococcus pyogenes was found in the lungs and liver, and in the pleural and peritoneal cavities.

CASE 3. (Gyn. No. 415.) The patient was operated upon for a left tubo-ovarian abscess, from which streptococcus pyogenes was isolated. On the second day after the operation a peritonitis developed; the abdomen was reopened, and drainage was established. On the morning of the third day, the bronchi filled with mucus, and two hours afterward the patient died. Post-mortem examination revealed the following conditions: Pelvic abscess, seropurulent peritonitis and pleurisy, serous pericarditis, bronchopneumonia, necrosis of intestinal mucosa.

CASE 4. (Gyn. No. 636.) A panhysterectomy was performed for a sarcoma of the uterus. On the following day a pleural effusion took place. The patient gradually sank, and on the seventy-sixth day left the hospital against advice. She died at home on the following day. At the autopsy, metastatic nodules were found throughout the lung tissue and pleural cavities.

CASE 5. (Gyn. No. 2241.) Hysteromyosalpingo-oöphorectomy was performed. Patient had very thick abdominal walls. Operation lasted 3 hours and 35 minutes, 700 grams of ether being used. On third day, bronchopneumonia developed; no peritoneal or bowel symptoms. Died on fifth day, from an acute cardiac dilatation.

CONCLUSIONS

Pulmonary complications after abdominal operations may originate in several ways.

1. Generally from an infection originating from the field of operation.

2. From the effects of the anæsthetic:

(*a*) From the administration of too great a quantity of the drug, exhibited over too long a time;

(*b*) From the inspiration of vomited or infective material — inspiration pneumonia;

(*c*) From injurious substances contained in an adulterated anæsthetic.

3. Exposure, either during or after the operation, to sudden or excessive changes of temperature.

4. In 1007 abdominal operations, 35 (or 3.5 per cent) of our patients developed pulmonary complications.

5. Older patients do not show more susceptibility to lung complications than the younger ones.

6. Only 4 of the 35 patients showed physical signs of lung involvement before operation.

7. In three cases, acute pulmonary tuberculosis was evident immediately after the operation.

8. Out of the 35 patients, 5 (or 14 per cent) died. In one case a bronchopneumonia, in a second a general peritonitis, and in a third an acute cardiac dilatation were the immediate causes. In the other two cases metastatic nodules from malignant growths in the pelvis were found in the lungs.

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EPITHELIOMA OF THE VULVA.

A REPORT OF SIX CASES, WITH A REVIEW OF THE LITERATURE.*

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There are many essays on this subject, but the majority consist in a citation of cases with a very brief reference to the literature. Among the German and French writers, such men as Franke, Schwarz, and Maurel have produced excellent monographs, and from these works a considerable amount of the material for this paper has been derived. An attempt has been made to cover everything of importance in the entire literature, with a more minute analysis of the following 135 cases: Mayer,[37] 4; Arnott,[12] 2; Storer,[53] 1; Cushier,[11] 1; Aschenborn,[3] 2; Küstner,[30] 5; Simmons,[52] 2; Rupprecht,[49] 8; Manley,[34] 2; Janvrin,[27] 1; Maurel,[36] 27; Munde,[40] 1; Schmidt,[50] 2; Zeiss,[59] 1; Schwarz,[51] 23; Ingerman-Amitin,[26] 7; Leech,[32] 1; Hirst,[25] 2; Hart,[19] 3; Henry,[20] 1; Mracek,[39] 1; Kelly,[29] 4; Franke,[14] 16; Noble,[41, 42] 3; Butlin,[8] 3; Congdon,[10] 1; Peterson,[47] 4; Reed,[48] 1; Dittrick, 6.

The histories of the 6 cases that have been met with in the Lakeside Hospital will be given somewhat in detail:

Case I.—M. A. B., admitted to Lakeside Hospital August 17, 1898. The patient is sixty-eight years of age and has been married forty-one years. She has borne six children. One sister has "ulceration of the womb," but there is no other history bearing on malignancy in her family. Several months before admission the left labium majus began to enlarge; a nodule, which when first seen was the size of a bean and very hard, has been gradually growing larger. About three months later ulceration began. The discharge from it has been purulent, watery, and bloody. The growth has been more rapid during the last few months. The patient lost twenty pounds in weight during the summer. She has no discomfort with urination, and the urinary examination is negative. The treatment has consisted of local applications of salves.

On examination there is a bloody discharge issuing from the vulval tumor. On the left labium majus is a raw, ragged enlargement pushing the lips apart. The left inguinal glands are indurated and enlarged to the size of the end of the thumb.

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* From the Gynecological and Pathological Departments of the Lakeside Hospital.

The vulval tumor, with a considerable amount of surrounding tissue and the left inguinal glands, were removed by Dr. Dudley P. Allen.

Microscopic Examination. A considerable amount of purulent exudate is seen on the surface. The squamous epithelium is practically normal at one end of the section, but gradually becomes thicker, the cells dipping down into the underlying connective tissue in solid, branching processes. In the centre of the tumor there is a network of larger and smaller masses of these cells. Between the alveoli very little connective tissue is seen, and this is markedly infiltrated with leukocytes. The epithelial cells vary in size, staining reaction, and in the number of nuclei present. Nuclear figures are not numerous. There are many epithelial pearls seen. Many of the epithelial processes are necrotic.

A section through the mass removed from the groin shows a similar picture, with many epithelial pearls.

Diagnosis. Epithelioma vulvæ (cancroid), with metastases in the left inguinal glands. The patient had a recurrence in both inguinal regions six months later, and died as a result of hemorrhage from the left femoral vein August 1, 1899.

CASE II.—R. K., aged sixty-two years, widow. Admitted February 21, 1899. The family history is negative. She has had five children; the youngest being thirty years old. Menstruation ceased at forty-five years, and since then there has been no discharge. The urinary examination is negative.

Four months ago the patient noticed a pimple on the anterior surface of the right labium majus, which gradually increased in size. There was constant irritation about the nodule, and she frequently scratched it to relieve the itching. Two months later the surface became ulcerated. During the last month a small ulcer has appeared on the left labium at the point of contact with the larger ulcer. For three months micturition has been accompanied by intense pain.

On examination on the anterior surface of the right labium majus is an ulcerated surface, 1.5 cm. in diameter, elevated, extending inward toward the clitoris, with an area of induration about 4 cm. in diameter. This is very sensitive. Opposite this on the left labium majus is a small indurated ulcer. There is no apparent involvement of the urinary meatus.

The patient was operated upon by Dr. Allen. An elliptical incision, 10 cm. in length, was made, including both ulcerated areas, extending well up over the mons veneris and down through the labia minora almost to the level of the urethral orifice. The wound healed primarily on the right and by granulation on the left side.

The patient was discharged April 8, 1899, and readmitted July

14, 1899. She had noticed five weeks previously a lump in the right groin, which had steadily increased in size. This was very sensitive, and about the size of the little finger. There was also a small recurrence on the vulva. The glands in the right groin were resected together with the local recurrence. The vulval wound healed primarily. The inguinal wound healed by granulation and was discharging slightly when the patient left the hospital.

Microscopic Examination. The surface is covered with necrotic debris over an irregular base of epithelial cells, which send irregular branching processes into the underlying connective tissue. These cells vary greatly in size, some being ten times as large as others; in some the nuclei are round, in others oval. Some nuclei are small and stain deeply, while others are large, pale, and vesicular. Some cells have one nucleus; others have as many as four nuclei. Nuclear figures are not abundant, but several atypical forms are seen. Many cells show a keratohyaline degeneration. There are not many epithelial pearls. Some of the alveolar processes of these cells are very thick, while others are not more than two cells in width. Many large irregular masses of chromatin are seen in the cell nests. The connective tissue between the epithelial masses is scanty, embryonic in character, and densely infiltrated with leukocytes. Many areas of necrosis are seen in the connective tissues and also in the epithelial cell nests. The bloodvessels are numerous and have very thin walls.

Sections taken from the vulva and from the glands removed at the second operation show the same condition.

Diagnosis. Epithelioma vulvæ, with metastases in the right inguinal glands.

CASE III.—A. W., married, aged seventy-three years. Admitted September 16, 1903. The family history is negative. She first noticed a tumor on the right labium majus seven months before coming to the hospital. Under treatment this would heal over and then break down. It has been growing progressively larger, and from it there exudes an irritating seropurulent discharge. She has noticed a lump in the right groin for the last three weeks. On examination there is seen to be an irregular, hard, ulcerated, elevated, reddish patch of tissue, measuring 4 cm. by 2 cm., on the right labium majus. On the left labium there is a reddened area which has not ulcerated. On September 18 Dr. Allen excised the tumor and the surrounding tissue, together with the right inguinal glands. One of the latter was necrotic in the centre. The vulval wound healed readily, and the incision in the groin, which was drained, rapidly granulated in and was almost closed when the patient was discharged, September 28, 1903.

Microscopic Examination. The tumor is made up of masses of epithelial cells, invading the entire connective tissue. The cells have the irregular appearance belonging to an epithelioma. Epithelial pearls are very numerous, as many as fifteen being seen in one field under the low power. Many areas of necrosis are seen in the alveolar processes and also in the connective tissue. Many cell nests have dropped out of the section.

Sections through the inguinal glands show considerable necrosis. The glands are extensively infiltrated with the epitheliomatous growth, which shows the same marked pearl formation.

Diagnosis. Epithelioma vulvæ (cancroid), with metastases in the inguinal glands.

Case IV.—B. K., single, aged fifty years. Admitted December 31, 1903. Menstruation was normal and ceased at forty-six years. In August, 1902, she noticed a growth on the right labium majus. Two months later this was removed, together with the right inguinal glands. Later the right groin became tender and painful, and in August, 1903, the swelling broke, and there has been a discharge from this region from that time. In September, 1903, she noticed a recurrence on the vulva (Fig. 1). She complains also of dysuria, insomnia, and pain in the thigh.

Examination. The right thigh is flexed and cannot be completely extended, while the entire limb is œdematous. Extending along Poupart's ligament, just beneath the skin, is an irregular nodular mass. In the centre of this mass is a small papilla, from which a fetid purulent discharge exudes. The greater portion of the right labium is missing. On the lower portion of the clitoris, just above the old scar, there is a small, plaque-like tumor mass, 2.5 cm. in diameter, and elevated 6 cm. above the surface. This is indurated, ulcerated, reddish, and granular in appearance, with small, whitish areas of necrosis over the surface. There is also a small, granular, ulcerated area in the left labium, where the latter comes in contact with the tumor.

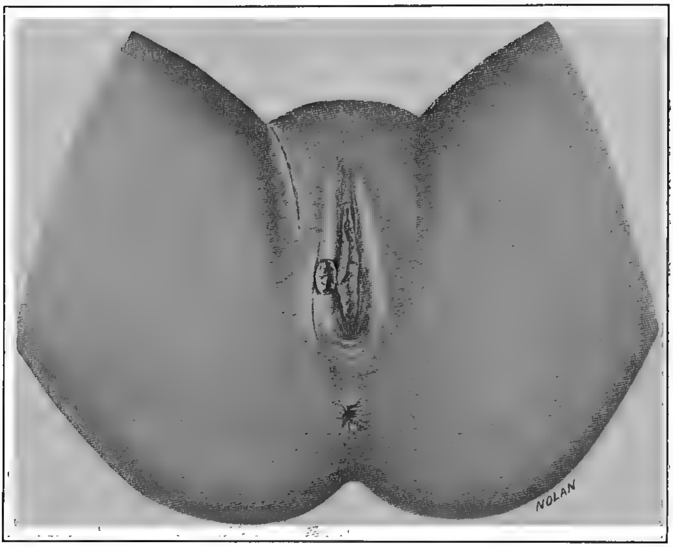
A small portion of the tumor was removed for examination, and an incision made into the mass in the groin to provide better drainage. In the latter situation a large cavity was found, which extended very close to the femoral vessels.

While the patient was in the hospital several nodules developed in the skin. Two of these were in the abdominal wall, 3 cm. above the mass in the groin, while five were seen scattered over the front and inner side of the right thigh, from 3 cm. to 15 cm. below Poupart's ligament. These nodules were hard, irregular, and reddened, from 0.5 cm. to 1 cm. in diameter, and did not move beneath the skin.

The groin was dressed daily, and three times a week, for two months, the patient was submitted to the *x*-rays. This procedure had very little effect on the discharge, and the pain still continued as before. The labial tumor, however, gradually became less prominent, and was almost level with the adjoining skin when the patient was discharged. The process beneath the skin did not seem to be at all checked. The patient left, against advice, on March 5, 1904, and died April 16, 1904, from exhaustion.

Microscopic Examination. The tumor is made up of masses of large irregular cells, varying in size and staining properties. The nuclei are large and oval, with large granules and one or more nucleoli. Typical and atypical karyokinetic figures are seen, but these are not numerous. A few prickle cells are seen in the cell nests. The epithelial cells are found in small collections in the connective tissue beyond the margins of the large processes. Epithelial pearls are very numerous. The connective tissue is very scanty, but shows a marked infiltration, with eosinophiles, polymorphonuclear leukocytes, and plasma cells. A few small areas of necrosis are seen.

FIG. 1



Scar from previous operation on vulva with small recurrence beside it. Old scar in right groin, showing the papilla from which pus was discharging.

Unfortunately, no sections were obtained from the lymphatic glands in the groin and the skin nodules, but these were undoubtedly metastatic deposits.

Diagnosis. Epithelioma vulvæ (cancroid), with metastases in the right inguinal glands and in the skin over the thigh.

CASE V.—E. G., married, aged thirty-two years. Admitted October 7, 1903. She complained of dull pains in both iliac regions, bearing-down pains in the pelvis, and a tumor on the vulva. The pelvic symptoms were due to adherent tubes and ovaries, with retroversion of the uterus. The family and personal histories were negative. About one year before admission she had noticed a "pimple" on the right side of the vulva. This has gradually grown larger and become painful. When irritated it would bleed. Caustics only stimulated its growth.

Examination. The inguinal glands of the outer group are just palpable on either side. On the inner surface of the right labium majus, rather low down, is a circular, fungating growth elevated 0.75 cm. above the surrounding level. It is granular and eroded on the surface. It is hard and apparently does not infiltrate the surrounding tissues (Fig. 2).

The patient was operated upon by Dr. W. H. Weir and the tumor removed by a wide excision. At the same time the adhesions about the tubes and ovaries were separated and the uterus was suspended after the Kelly method. She made an uninterrupted recovery, both wounds healing by primary union. She was discharged November 7, 1903.

Re-admitted May 5, 1904. One month before this a slight swelling had been detected in the right groin, which had gradually increased in size.

Examination. The outer group of inguinal glands are small and just palpable, while of the internal group one is markedly enlarged, measuring 2 cm. by 1.6 cm. There is no recurrence on the vulva.

The right labium majus and minus were excised. An extensive dissection of the glands and surrounding fat was carried out. A large gland, the size of a hazel-nut, was removed. Another, about the size of a pea, was found along the inner border of the femoral vein. In removing this the femoral vein was wounded, requiring the suturing of the wall at one point. All the fatty tissue was removed as far out as the inner border of the sartorius muscle and as deep down as the femoral vessels. The wound, which was closed without drainage, healed readily, except at the upper angle, where union took place by granulation.

Convalescence was slow, on account of pain down the leg, but this had almost disappeared when she was discharged June 22, 1904. When the patient was last seen (September, 1904) there was no sign of recurrence.

Microscopically. The gradual change from the normal skin to epithelioma is seen. The tumor has not infiltrated as far as the cut margin of the section. It is made up of finely branching cylindrical processes of epithelial cells. The cells have the irregular characteristics of malignancy. Numerous nuclear figures, both typical and atypical, are seen. Many areas of necrosis are apparent. The connective tissue is scanty, except at the margins of the sections. It is markedly infiltrated with leukocytes, many of which are eosinophiles. Epithelial pearls are numerous.

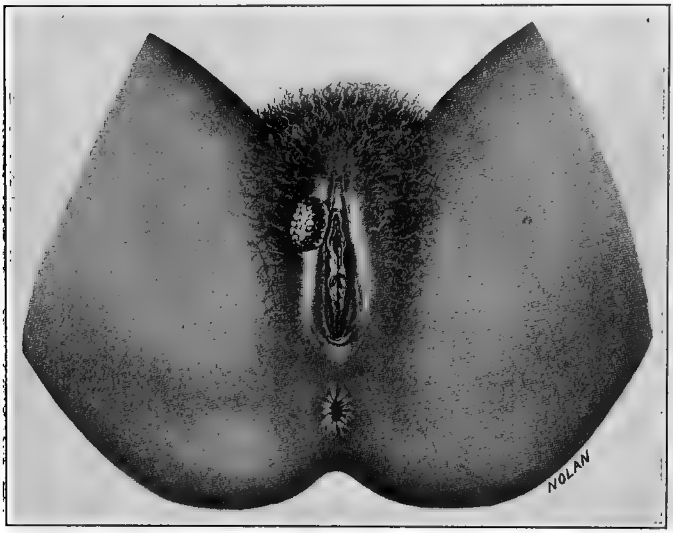
The sections removed at the second operation show the same process in the large inguinal gland, while all other sections are free.

Diagnosis. Epithelioma vulvæ, with metastases in the right inguinal glands.

CASE VI.—L. J., widow, aged eighty-one years. Admitted June 22, 1903, complaining of an offensive vaginal discharge, intense itching about the vulva, and a sensitive tumor in this region. The discharge is at times bloody and urination is frequent and smarting. The family and previous histories are negative. There has been a small nodule on the vulva for twenty years. The only treatment has consisted in cleansing lotions.

The patient is exceedingly well preserved. The inguinal glands are not palpable. The right labium minus presents an irregular, ulcerated, thickened area of tissue, measuring 2 cm. by 1.5 cm. This is sharply defined from the skin. The mass extends from the lower, inner edge of the labium minus to the urethral orifice. The clitoris is not involved. On manipulation the tissue bleeds readily, and small, whitish masses can be squeezed out on pressure. There is no involvement of the vagina or uterus (Fig. 3).

FIG. 2



Epitheliomatous nodule on the right labium majus.

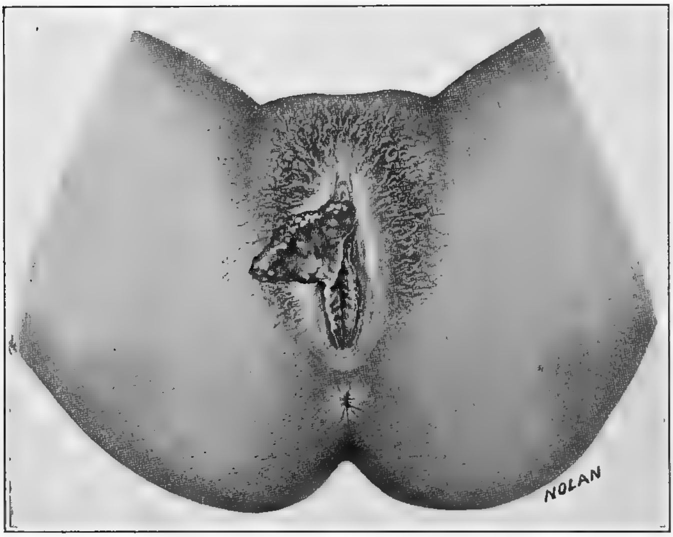
On June 25th Dr. Hunter Robb excised the tumor mass, together with a considerable portion of the right labium majus. The patient stood the operation well. The upper margins of the wound separated slightly, but healed by granulation. When the patient was discharged, July 25th, the wound was slightly congested and indurated.

Re-admitted November 2, 1903. Recurrence has taken place at the site of the old operation. She complains of sharp, darting pains radiating down the thigh; hemorrhage, profuse on one occasion; insomnia and dysuria. At the site of the right labium minus is an elevated ulcerated mass, 7.5 cm. by 2 cm. The left labium minus shows two distinct areas of ulceration.

On November 5th the mass was curetted and cauterized by Dr. Robb. This decreased the amount of discharge, and the pain was less severe. Two weeks later the growth again became active, the discharge being more profuse.

On December 22d the mass measured 9 cm. by 3 cm. Under anæsthesia the tumor was excised with considerable surrounding tissue. This was done in order to have as much of the disease as possible removed before beginning the *x*-ray treatment.

FIG. 3



Epitheliomatous growth, implicating the right labium minus and gradually extending.

January 4, 1904. There is a large excavated area on the right side of the vulva, measuring 7 cm. by 5 cm. by 5 cm. The outer wall of this cavity is made up of muscular tissue, normal in appearance, while from the floor and inner wall four irregular, fungoid masses are projecting. There is also a small metastatic nodule on the posterior commissure. At this time the *x*-ray treatment was begun. For three weeks this afforded marked relief. Immediately after the treatment the patient enjoyed from one to two hours' sleep, and was free from pain for from six to twelve hours. The large fungoid processes at first became blanched and then gradually subsided to the level of the wall of the cavity. The discharge became less profuse.

April 6th. *x*-ray treatment has been continued every other day. The skin about the growth is much thickened and browned from the treatments. The outline of the excavated area is irregular, and projections from the floor and walls are seen. The left labium is much enlarged and forms a hard, indurated mass, measuring 6 cm. by 2 cm. From the upper angle of this mass springs a hard, irregular growth, which extends over the abdominal wall above the symphysis.

9th. The patient was anæsthetized and a wide excision of the growth was made. The whole mass on the right side, which was adherent to the periosteum, was dissected off the bone. The left labium majus and labium minus and a considerable portion of the mons veneris were removed. A portion of the anterior vaginal wall was also removed from the right side. The wound was partially closed, drainage being employed above and below. Considerable inflammatory reaction followed, which was greatly relieved by daily hot sitz baths.

June 24th. The *x*-ray treatment has been continued, and seems to check the superficial growth, but beneath the skin the infiltration has progressed unabated. The *x*-ray does not now relieve the pain.

There is now an ulcerated area, measuring 11 cm. by 2.5 cm., at its widest point, over the right side of the vulva. There is a small sinus at the upper angle leading to a hard, infiltrated mass above the symphysis pubis.

The nodule on the posterior commissure is slightly larger; the ulceration in the vagina is still limited to the outer third of the anterior vaginal wall on the right side. The inguinal glands are not palpable. The patient was discharged June 24, 1904.

Re-admitted August 12, 1904. She is more cachectic. There is a rounded, sensitive mass over the symphysis pubis. The ulcerated area on the vulva extends 4 cm. into the vagina.

September 13th. The rounded mass over the symphysis (which had reached the size of a cricket-ball) was excised. It was found to be necrotic in the centre.

October 1st. The patient is daily becoming weaker. Her appetite is still good. Her pain is being controlled by morphine. The rectum, urethra, and inguinal glands are still free, and no evidence of metastases can be found in any other organs.

Patient died February 11, 1905. The autopsy revealed an extension along the deep inguinal and iliac glands on either side as high up as the junction of the common iliac arteries. Metastatic nodules were found in the bladder, the stomach, both kidneys, both lungs, left pleura, and the heart. This was confirmed by microscopic examination.

Microscopically. The tumor is made up of finely branching processes of epithelial cells, which are irregular in size and staining properties. There are from one to four nuclei in the cells, vesicular or deeply stained, and containing from one to four nucleoli. There are no epithelial pearls. Both regular and irregular mitotic figures are seen, although they are not numerous. The connective tissue is infiltrated for a considerable distance beyond the margin of the tumor. Many of the connective-tissue cells have deeply staining nuclei, but none show nuclear division. The connective tissue is extensively infiltrated with leukocytes. Tissue from the second operation shows irregular epithelial processes made up of large cells, which in most places have oval or round, vesicular nuclei. There are numerous concentric cell nests with pale centres, but these are not as hyaline in appearance as in epithelial pearls. Tissue from the third operation shows a few epithelial pearls, while nuclear figures are more abundant. There is very little stroma between the epithelial processes. Tissue from the later operations shows the same features as in the last specimen.

Diagnosis. Epithelioma vulvæ.

FREQUENCY. Cancer of the external genitalia of women is a rare disease. Franke, in May, 1898, found records of 15 cases primary in the clitoris. Veit[55] refers to 4 cases primary in Bartholin's gland. Percy[46] has recently collected 16 cases of primary carcinoma of the urethra. Sarcoma, melanosarcoma, myxosarcoma, fibrosarcoma occurring on the vulva are relatively rare.

According to Virchow,[56] cancer occurs in men and women in the proportion of 9 to 11. Willigks,[58] in 5536 autopsies, found cancer in 477; 190 of the subjects being males and 287 females. Gusserow[14] met with carcinoma in men and women in the proportion of 25 to 61. Among 8500 female patients, L. Mayer[38] had 332 malignant tumors, distributed as follows: 119, or 1.5 per cent., of the uterus, predominating in the cervix; 146, or 1.7 per cent., of the uterus, with involvement of the vagina; 256, or 3.2 per cent., of the uterus; 8, or 0.09 per cent., involving the vagina without the uterus; 10, or 0.1 per cent., of the vulva; 2, or 0.02 per cent., of the ovary; 8, or 0.08 per cent., of the breast; 39, or 0.45 per cent., in other than the sexual organs.

Gürlt[18] arranged the following table indicating the incidence in 11,140 benign and malignant tumors in females, 7479 of which were carcinomatous. Of these, 2845 were in the uterus alone; 604 in the uterus and vagina; 114 in the vagina alone; 81 in the vulva; 71 in the ovary.

Schwarz met with 1 vulval carcinoma to every 38 uterine carcinoma, Virchow[56] 1 to 35 to 40, and Gürlt[51] 1 to every 48 in the uterus.

Gönner[17] found, among 900 gynecological patients from 1873 to 1881, 99 with carcinoma, and in 9 of these the vulva was the primary seat. Eisenhart[13] found, among 658 gynecological patients, 2 with primary vulval carcinoma.

Billroth,[6] in eight years, met with 4 vulval carcinomata among 548 cancer cases.

In 2134 gynecological patients admitted to Lakeside Hospital, there have been 106 cases of carcinoma of the generative organs, distributed as follows:

Cervix uteri	72
Fundus uteri	8
Vagina	2
Ovary	18
Vulva	6
	106

Carcinoma of the vulva has occurred in 0.28 per cent. of our gynecological patients, and forms 5.66 per cent. of the cases of carcinoma of the female generative organs. These figures represent fairly accurately the relative frequency of this condition, for by combining the cases reported by Mayer, Gönner, Eisenhart, and those presented in this paper, 27 cases, or 0.22 per cent., were found in 12,192 gynecological patients.

According to Gürlt,[18] carcinoma of the vulva formed 10 per cent. of all cancers in the female. His findings are based on observations covering 11,140 benign and malignant tumors.

Age. Sarcoma of the vulva occurs at an earlier age than carcinoma. Launois,[36] however, reported a case of sarcoma in a woman aged sixty-two years.

Carcinoma, on the other hand, occurs at the end of the activity of sexual life. The oldest patient was ninety years, the youngest twenty years, and the average was seventy years. In 84 per cent. the patients were over forty-five years, the usual time for the menopause.

Every author who has written on this subject quotes West's[57] case in a woman, aged thirty-one years, as the earliest appearance of carcinoma of the vulva. There are, however, 4 well-authenticated cases in patients aged thirty,[51] thirty,[41] twenty-nine,[32] and twenty[2] years, respectively, the diagnosis in the second and the fourth having been confirmed by microscopic examination.

In 126 cases in which the age was given they were divided as follows:

Age.	Cases.	Per cent.
20	1	0.8
21 to 30	3	2.4
31 " 40	12	9.5
41 " 50	24	19.0
51 " 60	28	22.2
61 " 70	41	32.6
71 " 80	14	11.1
81 " 90	3	2.4
	126	100.0

Winckel[14] gives the following statistics on 54 cases:

Age.	Per cent.
30 to 40	9.7
41 " 50	25.8
51 " 60	32.2
61 " 70	25.8
71 " 75	6.5

Mayer's[14] statistics are:

Age.	Per cent.
20 to 30	4.51
31 " 40	22.93
41 " 50	24.19
51 " 60	20.68
61 " 70	9.03
71 " 80	1.13

Mayer finds the greatest frequency in the fifth decade, Winckel in the sixth, and our own figures, based on a much larger number of cases, in the seventh decade. The ages of the individual cases were as follows: Twenty, twenty-nine, thirty (2), thirty-one, thirty-two (2), thirty-four (2), thirty-five, thirty-six, thirty-seven, thirty-eight (2), thirty-nine, forty, forty-three (2), forty-four (2), forty-six (2), forty-seven (5), forty-eight (2), forty-nine (6), fifty (5), fifty-one (3), fifty-two (2), fifty-three, fifty-four (5), fifty-five (4), fifty-eight (6), fifty-nine (2), sixty (5), sixty-one (3), sixty-two (6), sixty-three (2), sixty-four (3), sixty-five (5), sixty-six (4), sixty-seven, sixty-eight (6), sixty-nine (2), seventy (9), seventy-one, seventy two, seventy-three (3), seventy-four (5), seventy-five, seventy-six (2), seventy-eight, eighty-one, eighty-four, ninety.

ETIOLOGY. In speaking of the etiology, the cause of cancer in general will not be considered, but only those conditions which predispose to its appearance on the vulva.

The principal factors, as usually quoted, are mechanical injuries and sources of chronic irritation. The latter class includes many and varied conditions; the former has to do with trauma incident to pregnancy, coitus, and accidental injuries. One would think that if direct injury had anything to do with the causation of carcinoma, it would sometimes follow difficult instrumental deliveries; yet in only 3 cases is pregnancy spoken of as a possible causative agent. Aschenborn[3] details a case that seemed to begin after a labor, while in the second case, cited by Franke, the tumor had been first noticed sixteen years before, at the first confinement, and after each labor it had increased markedly in size. In another of Franke's cases the patient had undergone eleven deliveries with forceps, but the disease was not definitely ascribed to the trauma connected with them. Coitus, too, may be attended by very severe injuries. Nussbaum[44] cites 2 cases in which the abdominal recti muscles were ruptured. Himmelfarb[23] quotes 2 cases of extensive laceration of the vaginal wall, 1 of which was followed by infection and death. Schulein[14] had 2 severe cases of laceration of the hymen. Other cases are mentioned by Bohm,[14] Franke,[14] Zeiss,[14] Teuffel,[14] and Berthel Anderson,[14] but the etiological relation to epithelioma of the vulva is not clear.

West[57] reports a case referred to a fall against the edge of a chair, with profuse hemorrhage five months before. In the monograph by Ingerman-Amitin, a case is described in which the patient fell on a chest and suffered from a considerable tearing of the right labium. Two years later a carcinoma developed at the site of the injury.

Although it can be readily seen that the vulva is exposed very often to severe injuries, very few of these accidents are followed by malignant disease. Since 2 of the cases reviewed in this paper occurred in women in whom the hymen was intact, it is clear that there are other factors that must be taken into account.

Other conditions concern the lowering of the local resistance and the keeping up of a chronic irritation. In looking over the histories of these cases, one of the most striking features is the number in which pruritus has preceded the carcinoma. In 27 cases (20 per cent.) the patients had suffered from this condition for from one month to five years before there was any sign of a tumor.

Of course, in those instances in which the irritation has preceded the tumor by a few months only it must undoubtedly be regarded merely as an early symptom. Where, however, the patient had suffered for several years from an itching, which has given rise to considerable scratching with some abrasion and pigmentation, and later a carcinoma has developed on this area, it is only fair to assume that the pruritus was at least an indirect agent in its production. Where small papillomata, which are frequently met with on the vulva, are associated with a long-standing pruritus, it is not difficult to understand how the constant irritation of scratching could start up a malignant growth. This is well illustrated in Case VI., in which such a tumor had existed for twenty years, and in which, for a long time, there had been an annoying pruritus. For two years this had shown active growth, and at the end of that time was a typical epithelioma.

In a case reported by Noble, pruritus had been present for twenty years, while the patient had only known of the existence of a tumor a short time. Kelly speaks of a case in which pruritus had been present for four years, and a spot like proud flesh was noted only two months before the patient came to him. Franke thinks that either the senile or diabetic form of pruritus may be followed by carcinoma. This is probably true as regards the senile form. In none of the cases was there a preceding history of a glycosuria, so that diabetic pruritus cannot be considered as a causative factor. But whether pruritus is an etiological factor or merely an early symptom, it should always be remembered that intense and obstinate itching is frequently the forerunner of malignancy, and whenever such a symptom is present a thorough examination with close inspection should be made.

In most essays there is very little mention made of leucoplakia in this connection. Hildebrandt,[51] Schwarz, Butlin, Noto,[43] and Besc[5] have emphasized the fact that leucoplakia of the vulva often precedes carcinoma. The buccal leucoplakia seen in habitual smokers, and variously described as psoriasis, ichthyosis, or keratosis, is not infrequently the antecedent of carcinoma in this region. Similar plaques are seen on the vulva and may be the precursors of epithelioma. These areas are irregular in circumference, opalescent, and pearly in appearance. They are situated on the labia majora or minora, clitoris, or even on the vaginal wall. Very often they are seen about advanced carcinomata and do not tend to disappear. Szasz[54] (Budapest) says that leucoplakia is a natural evolution between kraurosis and carcinoma.

Louis Mayer [51] has demonstrated a case in which carcinoma began in the epithelial thickening in the centre of one of these patches of leucoplakia. Schwarz reports a case in which a cancroid developed on the site where one year previously he had noted a leucoplakial patch about the size of a dollar. The diagnosis was verified by microscopic examination. Jouin[28] cites a case in which white plaques had been present a long time before ulceration began, being found constantly for two years. Franke, Maurel, Schwarz, Kelly, and Butlin have also seen leucoplakia of the vulva and vagina associated with carcinoma of the vulva. Since, then, carcinoma has been known to develop on areas of leucoplakia, they should be watched very carefully, and on the first suggestion of malignancy they should be widely excised.

Psoriasis is also mentioned as a precedent condition. Maurel quotes such a case in the practice of Dr. Saint-Philippe, where for fifteen or twenty years there had been psoriasis of the vulval mucosa, giving rise to some secretion and very painful itching. During the last four months an epithelioma developed, and six months later there were metastases in the inguinal glands.

Brittauer[7] reports a case of kraurosis vulvæ, which, from scratching to relieve the pruritus, became ulcerated, and, according to his description, probably malignant.

Lancial[31] reports a case of primary carcinoma of the left labium majus following a chronic abscess. This reminds one of carcinoma of the breast, which in some instances has been attributed to a chronic mastitis.

Arnott[30] has seen a case associated with syphilitic ulcer. Hutchinson says that old sites of syphilitic areas may become cancerous. Maurel quotes him as follows: "Syphilitic ulceration with inflammation and hypertrophy may degenerate into cancer in a way so imperceptible and gradual that it is impossible to say when one ends and the other begins."

According to Veit,[55] repeated infections with gonorrhœa and syphilis predispose to carcinoma. It is interesting to note, however, that none of the patients ascribed their condition to irritation from a vaginal discharge.

Masturbation associated with pruritus is mentioned by Ingerman-Amitin as preceding carcinoma. Two other cases are mentioned by the same author as being due to continued irritation. In one the condition was ascribed to the chafing from wearing a truss, and in another to continually rubbing the parts against the side of a bed. L. Mayer[37] also had a case in which the origin dates back to irritation from a truss. In this same connection, Schwarz has found similar factors in the production of primary vaginal carcinoma. Zizold[60] reported a case in which the carcinoma developed in a prolapse of the vagina, where the parts had rubbed against the inner surface of the thigh. Hegar,[51] Winckel,[51] and Kaltenbach[51] have reported cases occurring from the pressure of pessaries. Schwarz had a case in which a pessary had remained undisturbed for a year. The woman had a sudden profuse hemorrhage, and on examination the pessary was found completely encrusted by an extensive carcinoma, which had developed in the region of pressure.

FAMILY HISTORY. In only one case has any mention been made of malignant disease in the patient's family. The mother of one patient[29] died of cancer of the lip.

PREVIOUS HISTORY. One patient[36] was treated for six or seven years for a vaginal eruption, which first appeared at twelve years of age. Sixteen years previously a second patient[36] had had eczema of the scalp, followed some months later by icterus. Another patient[47] had had a tumor of the larynx removed eleven years previously, with no return. One patient[36] lived amid inferior hygienic conditions. One patient[14] had had puerperal fever, and two[14] had been curetted.

ASSOCIATED CONDITIONS. The following associated conditions were found: leucoplakia in 8 cases; retroflexion in 5; retroversion in 5; pelvic peritonitis in 2; psoriasis in 2; descensus uteri, double hernia, cervical polyp, femoral hernia, dropsy, fibroid and ovarian tumors, and adenoma of the right breast in 1 case each.

CHILD-BEARING. There were 97 patients married, 8 single, and 10 widowed. In 59 cases where the number of pregnancies is given, they were divided as follows:

Para	1	2	3	4	5	6	7	8	9	10	11	12
Number of cases	6	9	12	[illegible]	4	6	3	4	2	1	1	2

In 1 case there was a history of a twin pregnancy,[30] and in another there was a laceration of the perineum. One patient[14] had had eleven confinements, in all of which the forceps were used.

Occupation does not seem to play any part in this disease. In none of the cases is there any stress laid on this point.

SYMPTOMS. Epithelioma of the vulva may exist for a long time without causing any symptoms, and very often the tumor is only discovered accidentally. In 20 cases the presence of a small tumor was noted as the first evidence of the disease. In the majority of instances (44 in the series) the first sign of the disease was *pruritus*. This is variously described as an itching, burning, pricking, or sticking sensation, coming on in paroxysms, or sometimes constantly present. The discomfort is very intense and gives rise to considerable scratching, producing excoriations and pigmented areas about the vulva. It may disappear entirely for a time and then recur.

Ingerman-Amitin made the following statement: "It is possible that the origin of a small unnoticeable carcinomatous nodule may cause itching, which can exist as the only symptom for a long time, without the patient or even the doctor knowing the true condition."

The pruritus is due to the irritation of the nerve endings of the ilioinguinal and cutaneous branches of the pudic nerves. Noble[42] carefully dissected out these nerves in a case of epithelioma of the clitoris, and the itching was promptly relieved. Schwarz calls attention to the worried and anxious facies due to this uneasiness about the vulva.

Pain is one of the later symptoms, although it was the first cause of complaint in 6 cases. The tumors, when seen early, are usually neither painful nor sensitive, but the pain increases in severity as ulceration advances. The pain is described as sharp, piercing, darting, pricking, lancinating, stinging, smarting, or burning. It comes on in paroxysms, and is worse at night. It frequently radiates into the hip and down the thighs or may be referred to the lower abdomen or the vagina. Walking or even sitting is soon accompanied by great distress, and the patient becomes bedridden. Pain was marked in 46 cases, and in 7 cases there was no pain, but the latter were seen early in the disease. The pain was very severe in 3 cases in which the tumor had been growing for four months, while in others the growth had been present for more than a year.

Urination is nearly always interfered with as the carcinoma advances, owing to the trickling of the urine over the ulcerated surfaces. There was smarting, burning, scalding pain on voiding in 22 instances, and in many of these there was increased frequency. In advanced cases there may be incontinence. There may be difficult micturition from the fact that the surrounding infiltration causes a stenosis. Catheterization may be difficult, and there may be such a degree of retention as to force the patient to submit to operation.

Frequently, from the mere mechanical irritation of the tumor, there is a slight *discharge*, keeping the labia moist and causing discomfort. As soon as ulceration takes place the discharge becomes more profuse. At first it is whitish, mucoid, and watery, but later, as the tissue degenerates, it becomes more fetid, yellowish, and purulent. It is tinged with blood from time to time, and in 3 cases there was profuse hemorrhage. In 1 case *hemorrhage* was the first symptom; 45 patients complained of a discharge. *Painful coitus* was the initial complaint in one patient. An intractable insomnia very often results from the pain and discharge.

COURSE. Maurel describes a pre-tumoral period, which is accompanied by severe and intolerable pruritus, coming on at intervals in women who have passed the climacteric. The condition at the time, he admits, is unrecognizable.

In the second period, a tumor is present with infiltration about its margin, but without any ulceration. This tumor formation begins in two different ways. The first is characterized by a localized area of thickened and whitened tissue, the surface of which becomes cracked and fissured, and from these clefts the epithelial growth may spring. In the second class of cases the patient's attention is first directed to a prominent tumor resembling a "wart," "pimple," "blister," or "proud flesh." One meets with these small, warty prominences on the vulva frequently. Papillomata, Veit says, is the most fitting name for them. They resemble venereal condylomata, their etiology and failure of extension constituting important distinctions. These growths remain quiescent for months or even years, after which, from some cause, they may take a rapid growth and become typical malignant tumors.

Thirdly, we have the period of ulceration, and occasionally only at this time is the tumor first noticed. Involvement of the upper chain of the inguinal glands soon develop. The final stage is much more rapid. The ulceration becomes more marked. Occasionally metastases occur in the viscera. Death from exhaustion is the usual ending.

As a general rule, all the tumors are of slow growth. They may be latent for months or even years, until some accident calls the patient's attention to the vulva, and a tumor is discovered. A tumor had been present on the vulva for twenty, sixteen, and eight years, respectively, in three cases. The patients usually present themselves six or seven months after they have noticed the growth.

As illustrating the tardy growth the following cases are of interest: In one, after eight years, during the last six months of which the increase had been relatively rapid, the tumor measured 3 cm. by 3 cm. Other cases at the end of a year presented the following appearances: growth, the size of a filbert; ulcer, the size of a bean; three nodules, the size of a bean, 1 cm. in diameter; ten-pfennig-sized tumor; not ulcerated; two small, wart-like nodules.

The following showed a more rapid increase in size. After one year in one patient the growth had encircled the vulval outlet. In eight months another tumor had almost completely obstructed the vulval orifice. Another had increased to the size of a goose's egg in five months. Tumors the size of a hen's egg were found after six months, three months, and three weeks, respectively. In four weeks one tumor had reached the size of a dollar.

The average duration of the disease is about two years without operative interference. In one rapidly growing tumor the patient only lived four months after the tumor was discovered (Deschamps[12]).

In other cases the tumor may grow very slowly, and may not cause death for many years. In Case VI. a tumor had been present twenty years, and had grown actively for three and one-half years.

DIAGNOSIS. The vulva is the seat of other lesions, which are often difficult to differentiate from epithelioma.

In the early diagnosis, tuberculosis and syphilis are first to be eliminated. In tuberculosis or lupus under treatment the disease tends to heal with cicatrization, and often with considerable hypertrophy of the surrounding tissue. Tuberculosis occurs in younger patients and does not show as great a tendency to bleed on manipulation. When there is any doubt a small fragment should be excised and examined microscopically, as at times this is the only method possible to clear up the diagnosis.

When the disease occurs in the form of a prominent tumor it may resemble myxoma, sarcoma, or syphiloma. Sarcoma occurs early in life and is very rare. Early in the epitheliomatous process there is a close resemblance to the initial lesion of syphilis, but when the surface becomes ulcerated, the characteristic granular surface, the irregular, yellowish-white areas of necrosis, the hard consistency, the indurated border, and the resistance to antisyphilitic treatment, aid in the diagnosis. This feature was studied by Géber[15] in 1871. Four cases in this series were first treated for syphilis.

In the ulcerated form the lesion might be mistaken for a syphilitic or tuberculous ulcer, an ulcerated fibroma, or an ulcerated lipoma. Elephantiasis may have papillary excrescences resembling epithelioma.

Peterson reports a case that had been lanced, on the supposition that the growth was an abscess.

Psoriasis, which is indolent at the beginning, with very little itching or sensitiveness, may later be confounded with carcinoma.

When the inguinal glands are palpable, and there is rapid growth with cachexia, the diagnosis is more easily made.

PROGNOSIS. The prognosis is very grave. The fact that it occurs in women of advanced age, frequently limits the treatment to palliative measures, on account of other co-existing conditions, which contraindicate a radical operation. When the disease is seen before the inguinal glands are involved, the prognosis, of course, is more favorable. A radical operation at this time may give the patient several years of absolute freedom from the disease, although at any time it is likely to return.

PATHOLOGICAL ANATOMY. The primary seat may be on any of the structures comprising the vulva. In this series the following were first involved:

Labium majus	52 cases.
Clitoris	35 "
Labium minus	21 "
Anterior commissure	3 "
Posterior commissure	3 "
Vestibule	1 "

In 53 cases the disease began on the right and in 31 on the left side. The disease most frequently attacks the labium majus on the inner surface of its posterior half or in the sulcus between it and the labium minus.

In the beginning the disease occurs as a small warty tumor, a localized thickening, or even as a small ulcer. Later when the disease is more marked, Gebhard[16] recognizes three distinct types: (*a*) a prominent tumor; (*b*) a diffuse infiltration which is not elevated; (*c*) deep, crater-like excavations. Maurel describes two typical forms: (*a*) vegetating; (*b*) infiltrating. These two forms may co-exist.

In looking over 123 described cases, two-thirds were found to have occurred as a prominent tumor formation. In 23 per cent. there was a carcinomatous ulcer; 7 per cent. showed a crater-like excavation; 4 per cent. appeared as the diffuse carcinomatous infiltration spoken of by Gebhard. Two cases in the last class, when seen some months later, had developed eaten-out ulcers. The carcinomatous ulcers, through infiltration into the deeper tissues, with accompanying necrosis, later developed into necrotic cavities. Consequently when the disease is well advanced there are but two classes: those in which there is a prominent vegetating tumor and those in which there is ulceration, infiltration, and necrosis, extending deep into the cellular tissue.

In the different cases the disease presented the following appearances:

Duration of growth.	Prominent tumor formation.	Diffuse infiltration.	Depressed ulcer.	Crater-like excavation.
Six months or less	29	3	12	3
Six months to one year	17	...	6	2
Over one year	9	...	2	2
Time not stated	25	2	9	2
Total	80	5	29	9

About the site of the lesion the skin is frequently excoriated and pigmented from scratching, and plaques of leucoplakia are often seen. The larger number of cases are first seen when the process is represented by a prominent tumor. This varies with the progress of the disease from the size of a small bean, until it may completely block the vulval orifice. At first it is smooth, rounded, yellowish-white, sharply circumscribed, and freely movable over the underlying tissues. Occasionally it forms a flat, plaque-like tumor. Ulceration may be present as early as three weeks after the tumor has been noticed, or, in a small number of cases, there may be no ulceration for years. Usually, however, it is present at the end of six months. The ulceration begins on the inner and lower surface of the tumor, where it comes in contact with the structures of the opposite side. After this change has taken place growth is more rapid. The surface becomes irregular, uneven, raw, granular in appearance, and the color varies from pink to dark red or even violet. It may be nodular or fissured, and in the crypts between the small prominences are whitish collections of pus and epithelial debris. Small localized areas of necrosis give it the appearance of an erosion produced by an acid. The growth may be papillary or fungoid and consist of numerous densely packed papillæ, with mushroom-like edges. In consistence it is very hard and firm, except where there is much necrosis, when softish areas are felt. A more or less thickened pedicle may be present, especially when the growth arises from the clitoris.

The tumor bleeds readily on manipulation and is very friable. On section it is pearly white, with small yellowish areas of necrosis, which can be squeezed out on pressure. At first the tumor is superficial; later epithelial cords are felt extending into the deeper tissues through the lymph channels; the base is hard and indurated. Finally the growth becomes adherent to the os pubis and is firmly fixed.

More rarely the growth begins as a diffuse infiltration with no elevation above the surrounding tissue. It soon becomes ulcerated, and presents the usual appearance of a carcinomatous ulcer. When first seen the ulcer is usually about the size of a twenty-five-cent piece, and the growth is freely movable. The tissue about and beneath it becomes indurated and infiltrated, and the ulceration in the end involves one or both sides of the vulval orifice. The edges of the ulceration are irregular, elevated, and undermined. The base is reddened, moist, fissured, and has an eaten-out appearance. From the base papillary fungoid masses arise. Areas of necrosis are seen as whitish spots irregularly distributed over the floor.

The crater-like form is merely a more extensive degree of ulceration, in which the centre is deeply excavated from the penetration of the carcinoma into the underlying connective tissue.

Microscopically. Epitheliomatous growths of the vulva are divided into four classes: scirrhus and medullary carcinoma, cancroid and melanocarcinoma. The first two varieties are distinguished solely by the amount of intervening connective tissue; in the former the stroma; in the latter the epithelial tissue preponderates. L. Mayer[51] published 2 cases of the scirrhus variety. The microscopic descriptions are so few in the literature that it is impossible to tell how many cases are medullary in type. Four cases, 1 reported by Percheron[45] and 3 by Franke, seem to belong to this class. Cancroid is the term which the German authors use to represent the variety characterized by the presence of numerous epithelial pearls. Schwarz reported 23 cases. (This class forms the greatest number of epitheliomata of the vulva.) Deschamps[12] reported an instance of degenerating epithelioma in which some of the areas resembled colloid material. Numerous pearls were also seen, which would lead one to believe that it was a degenerating cancroid. Melanocarcinoma is characterized by the presence of brown or black pigment particles, either in the cancer cells or in the tissue about them. Bailly[4] and Franke have each reported a case of this kind. None of the cases belong to the glandular form of carcinoma, unless we include those in which the growth originates in Bartholin's gland. In 73 cases of this series the diagnosis was verified by microscopic examination, but in the others the descriptions, plates, and clinical histories show that they were undoubtedly epitheliomata. The progress takes place by direct extension along the lymph spaces, with degeneration of the adjoining tissue. In this manner the cutaneous tissues about the vulval orifice may be involved from the mons veneris back to the rectum.

Metastatic nodules are not infrequently found in the neighboring areas of the vulva or even back on the perineum, the infective material having been carried through the lymphatics, although in the latter case the cells have travelled against the lymph current. An interesting feature is also met with in cases in which the surface of the opposite labium, in contact with the tumor, becomes the seat of carcinoma. Cases of this nature are cited by Schwarz, Hildebrandt,[22] Zweifel,[56] and Kelly. Franke points out the origin as due to the invasion of the cancer cells through the blood or lymphatic vessels; mechanical irritation of the tumor itself; lowering of the local resistance from the secretions of the ulcerated tumor; direct transplantation of masses of cells; and the implantation of the organisms, if such there be, of cancer. There is no doubt that similar tumors arise at the point of contact, but the etiology in these cases is a matter of theory, and probably all but one of the causes assigned by Franke play a part. The parasitic theory, however, with our present knowledge is untenable.

Hildebrandt has said that carcinoma of the vulva only exceptionally extends beyond the carunculæ myrtiformes and the margin of the vulva. Schwarz says that conversely primary vaginal carcinoma rarely encroaches upon the vulva. In 14 cases the vaginal wall was involved, and in 2 cases[36] [51] the disease had extended along the entire length of the posterior wall and finally invaded the cervix uteri.

The urethral orifice is rarely invaded, but in 1 patient[50] the carcinoma had involved the urethra and the neck of the bladder. The cutaneous tissue, as far as the groove of the groin, had become infiltrated in 2 cases. The infiltration in 6 cases had extended upward beneath the mons veneris, and in 2 cases over the anterior abdominal wall. The clitoris was secondarily invaded in 17 cases, and the opposite side of the vulva in 11 cases. Small metastatic nodules are found in 2 cases in the skin over the inner surface of the thigh.[9] [36]

Metastases in the inguinal glands are very common. Through the communication of these with the iliac, sacral, and lumbar glands, metastases may be found in any of these groups. Percheron[45] describes such a case in which the inguinal glands were enlarged, and similar nodules were found along the iliac vessels and on up to the right of the aorta. In this case numerous nodules were also found in the lower part of the abdomen and on the posterior surface of the uterus. Cases in which the disease had involved the abdominal lymph glands are also reported by Küstner, Franke, Hirigoyer,[24] Saint-Philippe,[36] Schwarz, and Ingerman-Amitin.

Cases are reported in which other viscera have shown metastases, infection having probably occurred through the blood stream. In a case reported by Zeiss[59] there was a carcinomatous nodule in the left breast, with two infiltrated axillary glands. Küstner's[30] patient had miliary carcinosis of the lung, with carcinoma of the heart, liver, spleen, and kidney. Cancerous nodules were found by Arnott in the pleuræ, in both lungs and in the heart, the primary seat being on the clitoris. Franke had a case in which, from the clinical symptoms, he diagnosed metastases in the lungs. Léger[33] found in his patient cancerous nodules in the kidneys and lungs.

In those cases in which the glands were found to be carcinomatous, 50 per cent. had become involved during the second six months of the tumor's existence. One case showed involvement of the glands at the end of three months, another three and one-half months, and another in four months. On the other hand, a case reported by Frerichs[14] showed well-marked ulceration for three years with no glandular involvement.

In 33 cases clinically there was involvement of the glands, and in 9 of these the diagnosis was confirmed by microscopic examination. In 36 additional cases the glands were enlarged, but in 12 of these the condition was due to hyperplasia of the lymphoid tissue, without any carcinomatous invasion. Several cases showed slight enlargement of the glands before excision of the ulcerated tumor, and with the removal of the growth the swelling of the glands subsided. In 28 cases recurrence took place in the inguinal glands after operation. Where the glands from one side only had been removed in 2 cases, recurrence took place in those of the opposite side. In 7 cases there was a recurrence in the groin after the glands of the same side had been removed.

The disease may be so extensive in the inguinal glands that the blood supply of the leg may be interfered with sufficiently to cause œdema or even gangrene of the limb, as reported by Rupprecht.

Treatment. In cases which are seen before the glands have become enlarged a radical operation holds out the greatest hope.

Authorities do not agree on the treatment advised for the inguinal glands. Diffenbach[26] and Hildebrandt[26] hold that the new-growths are inoperable when the lymph glands are swollen. Winckel[26] considers excision of the glands a grave procedure on account of the patient's age, especially when they are bedridden. He asserts that exclusive excision of the primary growth is without doubt satisfactory. He employs this even when the superficial inguinal glands are enlarged, as this swelling usually subsides under such treatment. Other authorities remove the glands only when they become enlarged. Some take out only the glands on the side involved and remove those of the opposite side, if necessary, later. Rupprecht[49] advises removal of the glands on both sides, even though they may not be swollen. Veit says the inguinal glands should be removed before excising the tumor. As recurrence may take place on the opposite side of the vulva, or in the inguinal glands, on either side, it would seem better to take out the glands from both groins as well as both sides of the vulva.

When an excision of the primary growth only is to be carried out, the entire side of the vulva should be removed, but if there is the least suspicion of excoriation or induration, the opposite side should also be excised. The incision should be carried well outside the tumor from the mons veneris above to the posterior portion of the labium majus on either side. On the inner surface the incision is made just outside the carunculæ myrtiformes, the two incisions meeting a short distance above the urethra. Of course, this may have to be altered if the vaginal wall or the urethra is involved, and the incision must be made to include the entire growth. The mass so outlined must be dissected out, and the fatty tissue removed as deep down as the pubic bone. Maurel advises the use of the écraseur and cautery to accomplish this. When completed, Franke and Küstner have an inverted Y-shaped wound.

Rupprecht recommends extensive dissection of all glands, superficial and deep, analogous to the operation for cancer of the breast. His results justify the recommendation of the procedure as the best treatment for epithelioma of the vulva. The incision is carried from the symphysis pubis to the anterior superior spine. A second incision is made downward from the first, along the course of the femoral vessels. The skin is dissected upward to the aponeurosis of the abdominal muscles, outward to the fascia lata, and inward to the adductor muscles. The entire three-cornered mass of fat and glands is separated down to the deep vessels, after Scarpa's triangle has been cleaned out. The saphenous vein will have to be ligated where it joins the femoral. It is often necessary to divide Poupart's ligament and remove glands from the sheath of the vessels.

When the mass of fat and glands has been thoroughly dissected out on one side the other groin should be treated in a similar manner. These masses may either be removed singly or they may be taken out with the vulval growth in one piece.

In Case V. the femoral vein was wounded and the wall was sutured with silk. Leech tied the femoral vein in one case, and, although marked œdema followed, there was no gangrene. Langenbeck,[49] Bergmann,[49] and Braun[49] have tied the femoral artery. In such cases, Rupprecht advises the maintenance of the leg in the upright position with no compression.

Schwarz cites a case in which, on account of a heart lesion Olshausen excised the growth and both glands under cocaine.

As a rule, the wounds heal well, but on account of the great tension in some cases there may be some separation of the edges, with healing by granulation. The operation is attended by very little shock, and the patients stand it well. Among the complications after operation are secondary hemorrhage, infection, and bladder disturbances.

Secondary hemorrhage occurred in 2 cases, in 1 of which it took place from the artery of the clitoris. In a case reported by Franke, in which the posterior vaginal wall was involved, infection took place through the rectovaginal septum and fatal peritonitis developed. Where the urethral orifice is involved in the growth, a catheter should be left in the bladder. In 1 case, because of cicatrization about the urethral orifice, catheterization had to be kept up for a long time. Incontinence was present in 1 case.

When the disease is well advanced, only palliative measures can be employed. The ulcerated surfaces should be kept clean by daily dressings with antiseptic solutions. The hot sitz bath is especially useful in reducing the surrounding infiltration and the amount of the discharge.

Enough morphine should be given to relieve the pain and keep the patient comfortable. When the patient becomes bed-ridden, the greatest care must be taken to prevent bed-sores.

When the growth is fungoid, even though far advanced, thorough curetting with cauterization of the base will afford considerable relief for a short time. The *x*-ray, which has been shown to bring about complete healing of superficial epitheliomata of the face, has proved of very little value in this region. It was tried in 3 advanced cases; but, although the lesion was reduced from a prominent growth to practically a granular ulcer, the infiltration into the depths continued unabated. In one case, when this procedure was first employed, the pain was relieved for several hours after, but gradually this effect wore off, and the patient seemed to be as comfortable without as with the treatment.

RESULT. The longest period that a patient has been found to be entirely free from the disease is five years. This patient could not be pronounced cured, for, in a case reported by Schwarz, Olshausen excised a growth which had recurred six years after the patient had been operated upon by Küstner. Zweifel, in the *Cyclopedia of Obstetrics and Gynecology,* vol. xii. p. 311, cites another case in which a recurrence took place five years after the patient had been operated upon by Schroeder. It is evident that statistics showing freedom from recurrence for a shorter time than this are valueless, as far as permanent cures are concerned, and in the absence of any cases that have been free for more than six years, it must be admitted that the disease probably always recurs.

The following cases were free from recurrence for over three years, and 10 additional cases for more than one year:

Author.	Years.	Months.
Rupprecht	5	0
Martin[35]	5	0
Schwarz	4	5
Schwarz	4	5
Schwarz	4	1
Manley[34]	4	0
Schwarz	3	2
Schwarz	3	1
Zweifel[61]	3	0
Kelly	3	0

Schwarz had 2 cases, in 1 of which the patient died of emphysema, and in the other of erysipelas; they had been for four years and seven months and four years and four months, respectively, free from recurrence.

Martin[35] reports another interesting case in which, although the whole of the outer genitalia and one-third of the vagina had been removed, the patient went through a normal delivery two years afterward. The recurrence may take place either in the glands, on the vulva, or in both situations at the same time. Where the vulval growth alone was removed the recurrence was found in the glands in 12 cases, on the vulva in 9 cases, and in both simultaneously in 11 cases. Where the glands were removed from one or both sides, together with the primary growth, recurrence took place in the glands in 6 cases, on the vulva in 9 cases, and in both vulva and the glands in 7 cases. It is therefore necessary to remove the glands and the vulva as widely as possible in the endeavor to prevent recurrence. If, however, there is some contraindication to the more radical operation, it should be borne in mind that a wide excision of the growth will often yield several years of freedom from the disease. Nor should it be forgotten that, as in carcinoma elsewhere, the earlier the patient is submitted to operation the better her chance of having several years of freedom from a recurrence, even if permanent cure is impossible.

The most frequent cause of death is exhaustion, due to recurrence with ulceration. Five patients died from metastases in the viscera; 3 from hemorrhage from the femoral vein (Schwarz, Leech, and our own Case II.). Three patients died from other causes. In 2 other cases infection took place from the ulcerated tumor, and the patient died of peritonitis.

CONCLUSIONS. 1. Malignant growths of the external genitalia in women are rare. Carcinoma of the vulva occurs in approximately 0.22 per cent. of gynecological patients, and in 5.66 per cent. of patients suffering from carcinoma of the genital apparatus.

2. In a series of 135 cases, the records of which have been carefully examined, the age of the youngest patient was twenty years. The

greatest frequency is between the ages of sixty-one and seventy years.

3. Mechanical injuries to the external genitalia are generally quoted as among the principal causes of carcinoma vulvæ. Their etiological relation to this disease, however, is by no means generally evident. On the other hand, long-continued irritation, as, for instance, that caused by a pruritus, undoubtedly has often to do with malignant growths of the vulva. Leucoplakia also has often been noted as a precursor of epithelioma vulvæ.

4. The disease usually begins on the labium majus, and is seen more commonly on the right side.

5. There are two types of the disease—vegetating and infiltrating—which may co-exist.

6. There are four histological classes: scirrhous and medullary carcinoma, cancroid, and melanocarcinoma.

7. The most common symptom is itching. When ulceration has taken place there is usually pain, more or less foul discharge, and some bleeding. Occasionally there are profuse hemorrhages. Intractable insomnia often results from the itching and pain. Dysuria is not very uncommon.

8. Four stages are described by Maurel: (*a*) The pretumoral stage, characterized by an intolerable pruritus. (*b*) The second stage, in which a tumor with infiltration is present. (*c*) The period of ulceration, usually with speedy involvement of the inguinal glands. (*d*) In the final stage ulceration becomes more rapid. Occasionally metastases occurs in the other viscera, and the patient dies of exhaustion. The average duration without operation is about two years after the discovery of the tumor; not a few cases, however, last much longer.

9. When the diagnosis is doubtful, the microscopic examination will prove conclusive. Rapid growth, with cachexia and implication of the inguinal glands, is very suggestive.

10. The prognosis is bad. Return—so far as we know at present—is almost inevitable. No case is on record in which the patient remained free from a recurrence for over six years.

11. The best treatment consists in early excision of the vulva, with extensive dissection of the inguinal glands on both sides.

12. The *x*-rays are of little value in these cases. Occasionally they may alleviate pain and inhibit the external growth, but they exert no influence upon the deeper extensions. In non-operable cases the treatment is similar to that emplyed for extensive carcinomatous growths elsewhere.

I wish to express my thanks to Dr. Hunter Robb, Dr. Dudley P. Allen, and Dr. William H. Weir for the use of their cases and valuable assistance in preparing this paper.

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SUBCLAVIAN THROMBOPHLEBITIS FOLLOWING ABDOMINAL SECTION

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THROMBOPHLEBITIS is a complication occasionally found after abdominal operations, and in most instances occurs in the left femoral vein. The involvement of the left subclavian is very unusual, and in a hasty and imperfect review of the literature no similar instance was found.

The condition may occur as a primary affection in persons apparently in perfect health, and without any infection or dyscrasia of a gouty or other nature. Briggs, in the Johns Hopkins Hospital *Bulletin*, June, 1905, has collected a number of such cases. In one of these the subclavian vein was involved, and no infection, traumatism, or other assignable cause could be discovered.

As a complication it is frequently seen in infectious diseases, such as typhoid, pneumonia, influenza, pulmonary tuberculosis, syphilis, scarlatina, typhus, and gonorrhœa, also in gout, chlorosis, and acute articular rheumatism. In surgical cases it is apt to follow traumatism or varicosities of the veins, or infections in the area drained by the vein, or even infections in other areas.

After abdominal operations it occasionally occurs, and the left femoral vein is the one most frequently affected; if the left pelvic structures are subject to traumatism at the time of operation, the involvement of the left femoral can be readily understood, but it is more often affected than the right after operations upon the appendix or gall-bladder upon the right side of the abdomen. In fact, in phlebitis from any cause, this vein is the one most often involved.

The complication usually develops from one to three weeks after operation, and often occurs in so-called clean cases in which no pus has been found and during an ideal afebrile convalescence. Nevertheless, the consensus of opinion seems to be that the process is, as a rule, an infectious one, even if the presence of organisms cannot be proven. Welch, in *Allbut's System of Medicine*, vol. vi, gives a very thorough description of the pathology. The condition, whether from medical or surgical causes, presents the same characteristics. In the acute infectious diseases, such as typhoid, the specific germs are at times found in the thrombus or vessel-wall. More frequently the common pyogenic organisms occur, but careful examination of some cases has failed to show organisms either on culture or microscopic examination. In the usual pyogenic infections, the organisms are generally the same as in the original lesion.

Besides infection, various causes have been suggested, such as some interference with the force or volume of the circulation, changes in the composition of the blood, whereby its coagulability is increased, or the nutrition of the vessel-wall impaired, or the presence of toxines which might act in the same way.

The symptoms are pain and induration along the vein, œdema in the part supplied, and cyanosis of the skin. The superficial veins distal to the lesion are dilated with dark venous blood, and the affected vein can be felt as a firm, very tender cord. The progress is usually very slow, and the thrombosis may extend above or below the original lesion. If recovery occurs, the termination of the process may be by softening and disappearance of the thrombus, with complete restoration of the original channel, or the clot may organize, forming a firm fibrous cord and a collateral circulation be formed.

The treatment consists in absolute rest, to avoid the possibility of dislodging an embolus from the clot. This accident has frequently caused the death of the patient. Elevation of the part to favor the return circulation, and application of heat and gentle elastic compression are also useful. If local applications are employed, they should be very gently applied, without friction. Morphia or other sedatives may be required for pain. Later on, when danger of embolism seems past, gentle massage and passive motion may be begun to lessen the stiffness and to improve the nutrition of the part. Tonics are advisable, and, of course, the primary cause must be treated.

Most of the recent contributions to the literature deal with femoral phlebitis following abdominal operations. The whole subject has been fully discussed by Goodrich in the Brooklyn *Medical Journal*, June, 1905.

Vander Veer, in *American Medicine*, July 13, 1901, reports four cases of femoral phlebitis after the following "clean" operations: One appendix, one angioma of the liver, one uterine fibroid, and one bilateral ovarian tumor. In all these the left femoral was affected; in no case was there severe loss of blood or any infection apparent; primary healing occurred in each case, and the bowels were not constipated.

Meyer, in *Annals of Surgery*, 1901, quotes two cases following appendix operations, and reviews the literature. He believes the infection may originate in an old latent focus, as in interval appendix operations or from the alimentary tract.

Lennender, in *Centralblatt für Chirurgie*, May, 1899, noticed femoral phlebitis five times after appendicectomy, three times upon the left. He thinks mechanical obstruction has something to do with it, and therefore advises raising the foot of the bed throughout the convalescence. He ascribes the obstruction to the pressure of the abdominal binder upon the femoral vein, pressure of an overdistended rectum upon the left iliac vein, or it may be due to feeble circulation from weakness or anæmia.

Coe, in *Medical News*, July 1, 1899, reports six cases of post-operative phlebitis — three of the pelvic veins and three of the femoral — with recovery in all cases. He thinks it is really a septic process, although hard to prove.

Strauch, in *Centralblatt für Gynaekologie*, 1895, noted three cases of phlebitis in nineteen cœliotomies after he began the use of ether, and thinks that this may account for it, possibly by increasing the amount of carbon dioxide in the blood.

J. G. Clarke, University of Pennsylvania *Medical Bulletin*, vol. xv, No. 5, explains the left femoral thrombosis as beginning in the deep epigastric and passing backward through the external iliac. This would hardly explain an involvement of the left femoral if the incision were well to the right of the median line, as so often occurs.

The following case of subclavian thrombophlebitis occurred recently in my practice.

On December 9, 1905, I was called in consultation by Dr. G. Bowman to see a case of ruptured ectopic gestation. Both the history and symptoms were very typical, and need not be detailed. Her condition was very grave, and she was at once removed to Lakeside Hospital. It was decided to watch her very carefully to see if her condition would not improve somewhat before operation was attempted. Under stimulation with strychnia, submammary saline infusion, and saline enemata, with a small amount of morphia for the pain, her condition improved very markedly, although the vomiting was rather persistent. Two days after admission, an abdominal section was performed, a ruptured gestation-sac of the right tube was found, and a well-formed fœtus of about three months was lying free in the clots filling the pelvis. The left tube showed a chronic salpingitis with an occluded fimbriated extremity. The right tube and ovary, the left tube, and the vermiform appendix were removed, the clots washed out as thoroughly as possible, and the abdominal wound closed in layers without drainage.

She rallied well from the operation, and two days later had an attack of pain in the region of the gall-bladder, with transient icterus. Both rapidly subsided. Eight days after the operation, she complained of pain in the left axilla and shoulder, and in the supraclavicular fossa, with local induration and tenderness along the course of the axillary vein. The œdema and tenderness extended throughout the arm, and also involved the left side of the neck to the median line in the area drained by the subclavian vein. There were no cerebral symptoms, and there was no interference with respiration.

The pain was very severe at times, and occasionally required morphia. The arm was elevated, lightly bandaged with abundant cotton batting, and heat applied continuously.

Throughout the convalescence, localized areas of induration, more marked than that of the surrounding tissues, and exquisitely painful, would develop and gradually subside. One of these occurred on the anterior surface of the forearm, and another in the supraclavicular fossa.

The progress was very slow, but the condition gradually improved, and, after several weeks, gentle massage of the forearm, with passive motion, were instituted. At the present time, about six months after the operation, the arm is almost perfectly recovered, although it tires rather easily.

In searching for an explanation of the complication in this case, there are several possibilities. The Trendelenburg position was used, and the shoulder supports, although they were carefully padded, may have inflicted some traumatism, but there was no evidence of any injury due to them; they have been used for years in the operating-rooms at Lakeside, and never before have led to any trouble. The possibility of infection from the saline infusions must also be considered. Some of these were in the left submammary region, but there was no sign of any irritation around the punctures, and this area was but slightly involved by the subsequent œdema. The arms were not raised above the head, as is sometimes done with a patient in this position, so that no undue tension was exercised upon the vessels. The icterus and pain in the gall-bladder were very transient, and apparently independent of the trouble. The grave anæmia following the loss of so much blood and the hydræmic condition of the blood, which no doubt existed from the administration of the numerous infusions, might easily explain the phlebitis, as such a complication frequently occurs in certain forms of anæmia. There was no evidence of any pelvic or wound infection following the operation, and as far as the pelvic condition was concerned, the convalescence was all that could be desired. The temperature rose to 102.5° immediately after the operation, but gradually subsided. This could easily be explained by the absorption of the adherent clot in the pelvis, which could not be completely removed at the time of operation.

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ECTOPIC GESTATION, WITH ESPECIAL REFERENCE TO THE TREATMENT OF TUBAL RUPTURE.

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Lawson Tait, to whom gynecology is greatly indebted for his elucidation of the subject of "Ectopic Gestation," taught that rupture occurring not later than the twelfth week was the universal termination of tubal gestation. This view was apparently accepted without contradiction for a number of years, when, in 1887, Werth drew attention to the possibility of tubal abortion, and gradually the latter has come to be recognized as the more frequent outcome of tubal pregnancy.

Whitridge Williams, in reviewing the literature down to about 1903, stated that whereas in 1892 Schrenck found only 6 cases of abortion in 610 cases of tubal pregnancy collected from the literature, the more recent reports of Martin, Wormser, Mandl and Schmidt, Fehling and Glitsch, comprising 289 cases, showed that 78 per cent. ended by abortion and only 22 per cent. by rupture. According to Martin, "this termination is the general rule, spontaneous rupture occurring only in those cases in which occlusion of the abdominal end of the tube precludes the possibility of an abortion, or in which the ovum, being inserted in a hernia of mucosa, burrows directly through the tube wall."

Later reports by other authors vary within wide limits, some giving a lower and some a higher ratio of abortion to rupture. Thus, Runge, reporting 125 cases of recognized ectopic gestation from the Charité and Polyklinik in Berlin, states that there were 73 cases of tubal abortion (58 per cent.), 47 cases of rupture (37 per cent.), and 5 intact tubal pregnancies.

Bandler thinks that the proportion of abortion to rupture is probably as large as 8 or 10 to 1, and makes mention of 60 cases of pelvic hematocele in Schauta's clinic, 55 of which had formed after tubal abortion and 5 after rupture of the tube.

Hirst, giving a series of 74 cases of ectopic gestation says that in a large majority a tubal abortion had taken place.

Newell, in the *Medical and Surgical Reports* of the Boston City Hospital, for 1905, gives a summary of 60 cases of ectopic gestation met with during the previous five years. A careful pathological report was made in every case. All were cases of tubal pregnancy, the tube being intact in 14, abortion present in 22 (36.6 per cent.), and rupture of the tube in 22 cases (36.6 per cent.); rupture into the broad ligament was reported twice, but here the diagnosis was open to question, as the definite pelvic relations were not absolutely made out. The author recognizes that these figures do not agree with the ordinary statistics (that tubal abortion occurs in 75 per cent. of cases of tubal pregnancy), and attributes the discrepancy to the fact that the hematocele in tubal abortion is absorbed spontaneously in a large proportion of the cases, and that only such cases come to operation as present symptoms which demand interference.

In the *Pennsylvania Medical Journal* for September, 1906, C. P. Noble publishes an analysis of the 91 cases of ectopic gestation, which were operated upon by him during the previous sixteen years. His cases are classified as follows: unruptured tubal pregnancy, 7; ruptured tubal pregnancy, 14 (15 per cent.); tubal abortion, 70 (77 per cent.).

THE TREATMENT OF ECTOPIC GESTATION. It is hardly necessary to refer to the obsolete methods for a while in vogue which aimed at the destruction and the subsequent absorption of the products of an ectopic gestation through the injection of certain drugs into the fetal sac.

The application of electricity to the same end is likewise only to be condemned.

If we may judge from statistics, in no other field has surgery achieved more brilliant results than in the treatment of ectopic gestation. But it is so often difficult to give figures their "proper bearings," and it is so easy for writers to overestimate the importance to be attributed to this or that factor in their enumerations.

Two plans of treatment present themselves, viz., the expectant and the operative, methods varying widely according to the stage that the pregnancy has reached.

A. Martin has shown that 36.9 per cent. out of 265 cases of ectopic gestation recovered under an expectant plan, whereas 76.7 per cent. out of 515 cases recovered under operative interference.

Schauta, after a careful study of the literature (1891) found that 123 cases operated upon and 121 cases treated without operation, presented a mortality of 5.7 per cent. and 86.9 per cent., respectively.

However, we are inclined to the view of Herman who says, in the *British Medical Journal*, January, 1904, that there ought to be no question of a comparison of the two methods, as each mode has its own place, and, furthermore, we feel that every case should be looked upon and studied as "one unto itself."

The majority of observers have agreed that immediate operation is called for in one class of cases, viz., the early cases in which a positive or highly probable diagnosis of ectopic gestation can be made before rupture or any severe hemorrhage has occurred, and with this view I fully coincide.

The object of this paper is to consider the treatment of another class of cases regarding which there is still quite a diversity of opinion. We refer to those patients who we find in a state of collapse following the rupture of an ectopic gestation.

We shall cite the views of several recognized authorities, discussing different phases of these "border-line" cases, as they may present themselves.

The position taken by some of the authors in their writings is not clearly defined. Thus to quote from Kelly's *Gynecology:*

"Patients have been successfully operated upon in profound collapse, but I would rather wait a few hours, in some cases, if there are any decidedly encouraging signs of improvement, to gain a maximum effect from stimulation, and then to operate." What if the signs of improvement do not appear?

Williams in his text-book of obstetrics says:

"Whenever we see a possibly pregnant woman in a state of profound collapse, and presenting a deathly pallor of the face, a subnormal temperature, and other symptoms of intra-abdominal hemorrhage, immediate operation is demanded, unless, indeed, her condition is so desperate that death is imminent."

Malcolm Storer expresses his convictions as follows:

"In cases seen immediately after rupture—in collapse, and acute profound anemia, while recognizing that the waiting-policy has able advocates, I personally feel that I should prefer to operate at once, no matter how grave the condition, or, rather, the graver the condition the more prompt would be my attempt to reach the bleeding point. While twelve hours or so may give a patient some hope of recovery from the primary shock, we have no certainty but that meanwhile blood may be coming out of the torn tube quite as rapidly as we can introduce salt solution under the breasts."

According to Storer, one advocate of the waiting policy has expressed skepticism as to a woman's bleeding to death from a ruptured tube, saying that the hemorrhage will stop of itself when the patient is sufficiently exsanguinated. I must confess that I have come to believe that such a view is worthy of most careful consideration, and that it would be very difficult to show that other factors than the actual loss of blood do not play the main part in the fatal termination in such a case.

Storer does not think the risk that the shock of an operation may take away the woman's one chance compares with that of her bleeding to death. His rule is to get ready for operation, stimulating the patient meanwhile. If she reacts and holds her own, wait, but at the first sign of losing ground, operate. If there is no reaction, operate and give her one chance.

He reports 3 cases in which the patients were in collapse at the time of operation, 2 of whom he lost. In each instance, he states, a large quantity of blood was found in the abdomen, and bleeding was still going on from a ruptured tube.

Cullen has reported a similar case, in which 2.5 liters of blood were found in the abdomen, and from a small opening in the posterior surface of one tube enough blood was oozing to fill a teaspoon in one or two minutes. Recovery followed.

It will always remain a question in such cases whether the manipulations of the structures at the time of operation are not responsible for the hemorrhage, which is found "still going on."

Vineberg, in the *Medical Record*, June, 1906, reports a series of 53 cases operated upon by him, of which there were 14 instances where a very large quantity of free blood was present in the abdominal cavity, and the patients were "in a most profound anemia." In several of the patients there was no radial pulse at the time of operation. "It is amazing to see," says Vineberg, "how in these cases an apparently moribund patient can be brought to life by opening the abdomen rapidly, ligating bleeding vessels, and injecting saline solution into the veins of the arm." There was but one death in his entire series, and this from double pneumonia on the twenty-first day after operation.

Vineberg feels confident that some of the collapse cases are lost through overhaste on the part of the operator, time not being taken to see whether there is any further oozing.

Of the 60 cases reported by Newell, to which reference has been made, there were 12 patients who entered the hospital with marked signs of internal hemorrhage and shock. In only 2 instances, however, was death attributed to the latter cause. His total mortality was 9; tubal rupture being found in 7 of these cases.

Says this author:

"In cases which are first seen in extremis from shock and hemorrhage, a reasonable interval before operation should be granted to allow for the reaction which usually follows the cessation of hemorrhage. If, on the other hand, no improvement follows within a few hours, or if the patient's condition continues to fail, it may be taken for granted that hemorrhage is still going on, and immediate operation, followed by heroic stimulation, offers the best chance."

In Noble's 14 cases of ruptured tubal pregnancy there were 6 deaths. All were in bad condition at the time of the operation, a number were moribund, and in 8 the abdomen was filled with fresh blood. To quote from his article:

"With free and continuing hemorrhage, shock, and anemia, the prospect of such patients with operation is far from good, the mortality in this group of cases having been 42 per cent. Without operation, however, it would have approached 100 per cent. With a continuing hemorrhage operation is urgently demanded, and hemorrhage is usually persistent in cases of tubal rupture. In exceptional cases, in which a large amount of blood has been lost and the condition of the patient is serious, the question will arise as to whether operation shall be immediately performed or postponed until improvement has occurred. The proper course in such cases depends upon whether hemorrhage is continuing or has ceased, and also upon whether the patient is so situated that the operation can be performed immediately, should evidences of recurring hemorrhage become manifest.

Errors should be made upon the side of prompt operation rather than upon that of undue waiting."

Among the German writers we find advocates of both plans of treatment for the class of cases under consideration.

Von Winckel operates in all cases of free hemorrhage into the peritoneal cavity as soon as possible, and without regard to the shock to the patient at the time. He argues that while with the weakening of the heart's action in cases of severe hemorrhage the bleeding ceases, yet as soon as the heart begins to work better, a recurrence of the bleeding from the ruptured vessels sets in.

Bumm advises, in cases of free hemorrhage, immediate operation. If the pulse is small and frequent, operation should not be postponed for even one-half day; the worse the general condition the more promptly must it be done.

Fritsch expresses his views as follows:

"If a diagnosis has been made of internal hemorrhage from a recently ruptured ectopic pregnancy, absolute quiet until the operation is unconditionally necessary. I would question whether an ice-bag to the abdomen has any advantage. To give subcutaneous saline injections before the operation is also wrong; I advise them directly after the operation, likewise bandaging of the lower extremities.

"What course to take is difficult to decide upon, when one sees a case in which the anemia is marked. To be sure one can and must make an attempt to save life, but often we operate too late from extraneous reasons, not dependent on the physician. Between the time of making a diagnosis and the completion of the preparation for operation too much time is lost. So much blood is poured out that the patient is unable to endure the effects of an interference as significant as a laparotomy imposes. It will often depend on the incalculable, individual resistance and tenacity of life of the patient whether she withstands the interference."

From Ahlfeld we quote the following timely words:

"If rupture has occurred several hours before the patient is first seen, and she has recovered somewhat from the initial shock, so that the pulse can be plainly felt, it is a question whether it is not safer to keep the woman perfectly quiet; the blood poured out around the ruptured tube has probably come to surround the point of rupture as a tamponing mantle. Place ice-bags or sand-bags on the abdomen and support the patient's strength; above all, give her bodily and mental quiet.

"Be ready, however, to employ surgical interference should there be a recurrence of the bleeding."

To summarize somewhat: It is generally taught that in cases of tubal rupture in the early months of an ectopic gestation, death is almost invariably due to the hemorrhage that takes place, and accordingly the majority of surgeons advocate opening the abdomen as soon as possible and ligating the bleeding vessels. If the total number of deaths could be known that have followed immediate operations for tubal rupture it would be found a considerable one. Particularly is this the case in the country, or in other places removed from the skill of the expert. Therefore, when surgeons advise that all such patients should be operated upon immediately, it is easily to be seen why the treatment might be almost as dangerous as the pathological condition. Naturally, the physician in charge of such a patient would feel that an operation should be done at once and that he must do it. Very often, however, such a man has had little or no experience with the performing of an abdominal operation. Under these circumstances the patient's life might be sacrificed simply from the shock of the operation alone. In some instances also a fatal result might follow from the introduction of an infection. For my own part I believe that when we are called to see a patient who is suffering from a tubal rupture, in the great majority of instances the active bleeding has ceased. Now, if such a patient is given an anesthetic and an abdominal operation is carried out the immediate shock of the operation may well be sufficient to cause her death, but to this is added the risk of producing a fresh hemorrhage by the manipulation of the tissues. Undoubtedly in this way a certain number of the immediate or early deaths following the operation may be accounted for. As a rule, after opening the abdomen in such cases we find a considerable amount of fluid blood present, but it is not often that we see an actually bleeding vessel. When we find spurting or oozing from the rupture in the sac it is generally caused by the blood that has been held under tension in the sac. A large proportion of ectopic gestations are situated in the ampullary portion of the Fallopian tube, and when the embryo passes out through the fimbriated extremity of the Fallopian tube the amount of blood poured out at this time is seldom if ever enough to produce a fatal result. Most of these cases, therefore, would undoubtedly recover without any further serious symptoms. For this reason all statistics dealing with the number of deaths due to a ruptured ectopic gestation are somewhat fallacious. From my experience, in the clinical and experimental side of this work, for the past three or four years, I feel positive that a fatal result due to the loss of blood alone is exceptional. From our examinations also of a considerable number of ectopic sacs, in which a rupture has taken place, we feel sure that it will not often be found that the large vessels, such as the uterine and ovarian arteries, have been torn. During the past four or five years we have carried out with satisfactory results the following method of treating all of our cases of ruptured ectopic gestation. If there are signs of improvement in the patient's condition (and this in our experience always takes place) we keep the patient under further observation. The change for the better is brought about by carefully stimulating the patient by means of saline infusions under the breasts, and in some instances also by means of hot saline enemata.

If the patient is not vomiting or is not nauseated we administer a stimulant in small quantities by the mouth.

In addition to this, we give morphine hypodermically for the pain and the nervousness. External heat is also applied to the body, and the lower end of the bed is slightly elevated. The sulphate of strychnine is also given hypodermically in doses of $\frac{1}{10}$ to $\frac{1}{20}$ grain every half-hour or so according to the indications. While this treatment is being carried out the operating-room is prepared so that it can be used at a moment's notice. We have also carried out this treatment in those cases that we have seen for the first time at the patients' homes. Then, as soon as the woman had recovered from the shock of the rupture she was transported to the hospital, where an operation could be carried out at any time that the necessity might arise. Every patient in our series has gradually improved so that after two or three days, and in some instances after twelve days' time, the operative procedures have been carried out with very little if any shock to the patient.

Analysis of a Series of Twenty Cases of Ectopic Gestation. From an analysis of the 20 cases of ectopic gestation that have come under our personal observation, and received surgical treatment, we may summarize our findings as follows:

1. *Age of Patient.* The youngest patient was twenty-three and the oldest forty-three. Between the second and third decades there were 7, between the third and fourth decades, 12; 1 patient was above the age of forty.

2. *Previous History.* 14 patients had given birth to children; 4 were primiparous and 10 multiparous (2 to 6). There were 6 nulliparæ.

A history pointing to previous pelvic inflammatory disease was recorded in only 3 of the cases. Miscarriage had occurred in 10 patients.

There had been a cessation of the menstrual flow during a period ranging from five to twelve weeks prior to admission in 10 of the patients. In 2 an irregular flow had been noticed for a short time previous to the acute onset of the illness, and in the remaining 7 there had been no menstrual disturbance in 4; the history was unsatisfactory in 3.

3. *Present Illness.* This dated from four days to eight weeks prior to the time of admission. Exacerbations of the primary attack occurred as late as the day of admission in a few cases.

The onset of the attack was in nearly all cases with pain, which was described in 13 instances as being "sudden and sharp," generally in the lower abdomen, but in 1 case it was most intense in the epigastrium. In 3 patients the pain was of a "cramping" or "bearing-down" character, while in 4 it was spoken of as being merely severe. In a number of instances this symptom was chiefly localized to one side of the pelvis.

Pain continuous or increasing in severity to the time of admission was noted in nearly every case of tubal rupture; whereas, in cases of tubal abortion there was usually a history of recurring attacks of pain at intervals of a few hours to a day or so.

Fainting attacks had occurred in 4 instances, 2 of which were cases of tubal rupture, the other 2 of tubal abortion and pelvic hematocele, respectively. 5 patients had had nausea and vomiting. A bloody vaginal discharge, varying from a slight to a profuse flow, and beginning with the onset of pain, or some time afterward, was noted in 15 instances.

4. *Condition on Admission.* In 5 of our patients the condition was regarded as serious and contra-indicatory to immediate surgical interference. All of these showed evidences of shock, and a marked anemia was present, the lowest hemoglobin record being 60 per cent. The general condition of the remaining 15 patients was "fair" to good, none exhibiting symptoms, however, that called for immediate operation.

Signs on bimanual examination pointing to a probable ectopic gestation were noted in 8 of our cases. The temperature was normal or above in 18 patients, the highest being

101.4°; not definitely given in 1; 1 patient in collapse had a temperature of 96°.

5. *Time of Operation.* No patient was operated upon earlier than the day after admission (eighteen to twenty-four hours), and there were only 3 who came to operation so soon. In 1 of these patients a diagnosis of pelvic abscess was thought to warrant an early vaginal puncture. The other 2 patients were in sufficiently good condition to undergo a laparotomy at the time. The remainder of our patients were operated upon at periods ranging from three to twelve days after admission, the average being five days; 8 of the 17 being operated upon on the third day.

Of the 5 patients who were in a grave condition at the time of admission, operation was not considered advisable until the third, sixth, eighth, and twelfth day afterward, respectively, in 4 instances, the other patient being the one mentioned above as coming to operation on the day after admission.

6. *Condition at Operation.* It will suffice to say that of our 5 serious cases all but the 1 operated upon the day after admission showed considerable improvement in their condition over that when first seen. The usual measures of stimulation and keeping the patient quiet had been employed.

7. *Operation.* There were 14 patients treated primarily by abdominal section, 4 in whom only a vaginal puncture was done, and 2 in whom vaginal puncture was followed by abdominal section, in the one case immediately, in the other twenty-four hours later on account of a suspected continuance of hemorrhage. Of these latter 2 cases 1 was an instance of tubal rupture, the other of ovarian pregnancy.

Tubal rupture was found at operation in 9 cases, six times on the left side, three times on the right side. Tubal abortion had occurred in 4 instances; 3 were left sided. An intact tubal pregnancy was met with twice, on opposite sides. Pelvic hematocele was the diagnosis in 4 patients. The unusual case of an ovarian pregnancy has been mentioned. Adherent structures on the two sides called for a bilateral salpingo-oöphorectomy in 3 patients. A unilateral salpingo-oöphorectomy was done in 11 instances, and the opposite tube removed in 9. Both tubes were removed in 2 cases.

The appendix was found involved four times; once it was adherent, and in 3 instances was deeply congested. It was removed from 8 patients.

Clotted blood or bloody fluid or the two together in large quantities were found in the peritoneal cavity in 7 of the abdominal sections (6 tubal ruptures and one ovarian pregnancy). Where an estimation of the quantity is given, the figures vary from 700 to 1500 c.c.

We wish here to raise the question whether one can judge of the actual loss of blood to the patient from the amount of bloody fluid present in the abdomen, as some of the latter is probably a serous exudation resulting from an irritation of the peritoneum by the blood that escapes into the abdominal cavity.

Drainage was employed in 3 of the abdominal section cases, once by the vagina in a primary section, once through both abdomen and vagina, and once per vaginam alone, respectively, in the 2 celiotomies that followed vaginal puncture.

8. *Convalescence and Results.* 11 patients made an uninterrupted recovery—9 of the celiotomies and 2 of the vaginal punctures. In 2 of the section cases, 1 for an ovarian pregnancy, the other for tubal rupture, convalescence was slow; in both of these patients there was a marked anemia, and a left subclavian thrombophlebitis developed in 1 of them.

There were evidences of a right popliteal phlebitis in 1 section case. In another bronchopneumonia was a complication. Following abdominal section for tubal abortion a concomitant uterine pregnancy ended in abortion on the fourth day after operation. Infection of the abdominal incision took place in 1 instance—a tubal rupture. 2 of the patients treated by vaginal puncture for hematocele had a considerable elevation of temperature during the first twelve to fifteen days, and 1 of them a good deal of abdominal pain. Both were discharged free from pain, but with adherent, pelvic structures.

There was 1 death in our series. This occurred in a patient whose convalescence from a celiotomy for tubal rupture had progressed favorably to about the tenth day, when signs of ileus began. The abdomen was reopened on the next day; a volvulus and intestinal adhesions were found present. Death ensued one hour later.

9. *Pathological Findings.* There were 2 specimens of intact tubal mole. Associated with 1 of these there was a hematosalpinx of the opposite side. Expulsion of the ovum from the tube without rupture had taken place in 4 cases. Rupture of the tube was met with in 9 instances, 3 in the isthmic, 3 in the ampullar, and 3 in the infundibular portion of the tube, respectively. Evidences of pregnancy were conclusive in all of these cases. There was no instance of intraligamentary rupture. Well-preserved fetuses were found in 3 cases, the largest being 9 cm. long.

A case of ovarian pregnancy furnished a rare and interesting specimen. Partly embedded in the ovarian stroma was a blood clot the size of a walnut, sections of which showed chorionic villi. A very recent corpus luteum was present. The tube on this side was perfectly normal save for a slight interstitial salpingitis.

Salpingitis in both tubes was present in 8 cases.

A perisalpingitis on the opposite side to that involved was noted in 10 instances.

Tissue removed from the pelvis per vaginam confirmed the diagnosis of hematocele originating from ectopic gestation in 2 cases; in 2 other instances degeneration of the tissues made a pathological diagnosis inconclusive.

I am not prepared to state dogmatically that women do not bleed to death from hemorrhage following ruptured tubal pregnancies, but I am however, of the firm conviction that surgeons are losing many of their desperate cases from over-haste in operating upon them.

The idea that the abdomen must be opened as quickly as possible after seeing one of these patients in order to check the bleeding, which may or may not be going on, seems to have taken deep root in the minds of many gynecologists. If recovery has followed the interference, "we saved our patient;" was there a fatal termination, "the patient died from the previous loss of blood."

We feel that the enthusiasm over our "happy results" has carried us too far, and that a calming restraint to our ideas is needed.

Let us consider the factor of hemorrhage in these cases, and later other influences that may have a bearing on the question. Reports seldom state even in an approximate way the quantity of blood found in the abdominal cavity of the patient. Some say "a large amount," others "a very large quantity," terms which convey but little meaning. What we should like to have in these reports would be a fairly accurate estimation of the amount of blood found present, and in addition the weight of the patient. We would then be in a far better position to judge to what extent "the previous hemorrhage" has been responsible for the fatal issue in many of the cases.

Physiologists have estimated the total quantity of blood in the human body at about 7.7 per cent. of the body weight. Thus, a woman weighing, say, 130 pounds, would have a blood content of 10 pounds.

Now, "just what percentage of loss," to quote from Howell, "can be borne by the human being has not been determined, but it is probable that a healthy individual may recover without serious difficulty from the loss of a quantity of blood amounting to as much as 3 per cent. of the body weight." This, in a woman of 130 pounds, would be a loss of 4 pounds, or, approximately, 1650 c.c. We question whether so large an amount of blood, or at any rate much more, is found in the average patient of the above weight as a result of hemorrhage from a ruptured ectopic gestation.

We have recently been conducting a series of experiments on dogs, to see if we might not be able to throw some light on this phase of the subject.

It may be worth while to here state briefly some of our observations: In the bitch, as may be recalled, the uterus consists of the body or corpus and its two long horns or oviducts; in the latter fetal development takes place. The oviducts are connected anteriorly with the very short, slender Fallopian tubes; the outer ends of the latter lie very near the ovaries, which are situated posterior and dorsal to the kidneys. The uterine arteries are branches of the pudics, the latter coming from one of the two main divisions of the internal iliacs; they are vessels of considerable size, even as compared with the corresponding arteries in women. The ovarian vessels are, on the other hand, quite small.

With these anatomical differences in mind, a brief resume of the cases is herewith presented:

EXPERIMENTS.

Dog No. 1. Well nourished. Weight, 6.5 kilos. January 11th. Ether anesthesia. The abdomen was opened through a median incision 6 to 7 cm. long. Pelvic organs apparently normal. The outer end of the right oviduct was cut through, and the right ovary excised. There was no free bleeding at the site of injury. The incision was closed in layers. There was little variation in the pulse throughout the operation. Quick recovery from ether, and an uneventful convalescence.

Dog No. 2. Well nourished. Weight about 12 kilos. January 25th. Ether anesthesia. Median incision 4 cm. long. Pelvic organs appearing normal. The right broad ligament was cut through its entire extent, the uterine vessels being severed. There was active arterial hemorrhage, the blood welling up into the abdominal wound. Incision quickly closed in layers. At the end of the operation the mucous membranes showed a distinct blanching. Pulse 140, of small size. Dog conscious thirty minutes after being put to bed. A good deal of vomiting during first six hours. 26th. Dog is up and walking about, showing no signs of pain. This dog escaped from her cage several days later. She had made a good recovery, so far as we could judge.

Dog No. 3. Good condition. Weight about 10 kilos. In "heat." January 30th. Ether anesthesia. Median incision 4 cm. long. Pelvic organs appear congested. Outer end of left oviduct cut through and left ovary excised. The left uterine vessels were now cut across. Free bleeding from the latter and also the ovarian. Incision quickly closed in layers. At end of operation pulse of rather small volume; rate not obtained. Dog conscious soon afterward. February 2d, condition good. Dog disposed to remain quiet. February 6th. Dog bright and active, taking her food well.

Dog No. 4. Well nourished. Weight about 10 kilos. February 2d. Ether anesthesia. Median incision 4 cm. long. Pelvic organs normal. The uterine vessels on both sides were cut across. Very free bleeding. Incision quickly closed in layers. Pulse rapid but of fairly good volume. Dog conscious before leaving table. Given at once, $\frac{1}{3}$ grain of morphine hypodermically. Thirty minutes later dog was standing and drinking water greedily. 6th. Dog suffered apparently but little from operation. Today seems bright, but is not disposed to move about much. 16th. Dog has made an uninterrupted recovery.

Dog No. 5. In good condition. Weight about 10 kilos. February 6th. Ether anesthesia. Median incision 4 cm. long. Normal appearing, pelvic organs. The left ovary was excised, and the uterine vessels on both sides cut. There was the usual free hemorrhage. Immediate closure in layers. Dog conscious on reaching bed. Pulse not very rapid and of good size. Seen thirty minutes later, dog had changed position, but was then perfectly quiet. 9th. Dog has been doing well. Yesterday was eating. Today does not appear so bright. Does not object to being moved. Pulse and temperature good. 16th. Rapid improvement since last note. Dog now active.

Dog No. 6. This is same animal used in Experiment No. 1, *q. v.* February 9th. Dog has made a complete recovery from first operation. Ether anesthesia. Abdomen reopened through former incision. No free fluid or clotted blood found in peritoneal cavity. There were a few delicate adhesions about the pelvic structures. The right oviduct was enlarged and bent upon itself. In the left oviduct were two fusiform swellings, the one about 1.5 cm. from the corpus uteri, the size of a pigeon's egg, the other in the outer half of the oviduct, almost as large as a duck's egg, apparently filled with clear fluid. The uterus and oviducts were now removed in toto by one continuous cut of the scissors from side to side. Bleeding was profuse. Immediate closure in layers. At the end of operation pulse was hard to obtain; respiration shallow. Dog able to open her eyes. Seen fifteen minutes later, dog was standing on all-fours lapping water. 16th. Dog did not appear to suffer from operation. A few hours afterward was walking about in her cage. No sedative was given. At present seems to be in good condition. 25th. Dog has apparently made her second complete recovery. Incision well healed.

Dog No. 7. Same animal as No. 3, *q. v.* Dog has made complete recovery. Now bright and lively. February 16th. Ether anesthesia. Abdomen reopened through former incision. No blood found in peritoneal cavity. A few light omental adhesions. No pulsation could be detected in the stump of the left uterine artery, nor was there any clot around it. The right uterine vessels were now cut, and temporary closure of the abdominal cavity made by placing clamps on the edges of the divided peritoneum. At the beginning of the operation the pulse rate was 128. The dog was now kept under a light anesthesia. Fifty minutes after cutting of vessels the pulse rate began to show an increased rate, being at this time 136. A steady rise continued during the next thirty minutes, at the end of which time the rate was 156. The clamps were now removed from the peritoneum, and the blood found in the pelvis was carefully removed with gauze sponges. No clotting had taken place. From the cut uterine, active hemorrhage was still going on. No attempt was made to check the bleeding by pressure or traction on the vessel, but gentle application was made with a gauze sponge at the cut end of the artery. Cessation of the bleeding resulted at the end of about ten minutes. Twenty minutes later a subcutaneous infusion of salt solution (400 c.c.) was given. This was nearly all taken up in thirty minutes. It was given to see if the subsequent rise in the blood pressure would bring on a recurrence of hemorrhage from the uterine artery. No such effect was produced at the end of thirty minutes after the absorption of the saline solution. Gentle squeezing of the end of the vessel, however, was sufficient to expel the clot, which had formed and fresh bleeding began. The experiment was brought to a close at this point, the uterine artery ligated, and the incision closed in layers at once. The pulse rate at the end of the three and one-half hours, consumed in the observation, was 144. 25th. Dog has done well from day of operation. Is now as active as ever. The amount of blood lost during the experiment was estimated approximately, and found to be 240 c.c.

Dog No. 8. Young bitch. Poorly nourished. Weight about 4 kilos. Mucous membranes pale. February 25th. Median incision 6.5 cm. long. Uterus very small, the oviducts slender, cord-like structures. Evisceration of both ovaries; the uterus and oviducts in toto. There was very free bleeding from all the vessels. Immediate closure in layers. But slight change in pulse during operation. Fifteen minutes later dog appeared to be having a hard, shaking chill. Was conscious, but not able to hold up her head. 26th. Dog is bright, but moves very little. March 1st.

Dog appears to be gaining rapidly. Is now walking about her cage. Very anemic. Ether anesthesia. Abdomen reopened through previous incision. No free blood in peritoneal cavity. Omentum and intestines adherent in places to bladder, pelvic wall, and rectum; all easily separated. Around the stump of the uterus a small blood clot was adherent. No other clots found present. Forcible manipulations of the stumps of the uterine vessels produced no active bleeding, only an oozing. Dog went into sudden collapse. Revived by artificial respiration.

Dog No. 9. In good condition. Weight about 4 kilos. February 26th. Ether anesthesia. Median incision 6.5 cm. long. Total evisceration of intra-abdominal genitalia as in previous animal. Profuse hemorrhage. Immediate closure in layers. Mucous membranes became greatly blanched. At close of operation pulse rate was 180, shortly afterward becoming almost imperceptible. Soon after reaching bed dog was conscious, but made no attempt to move. March 2d. Dog is bright and fairly active. Mucous membranes quite pale. Ether anesthesia. Abdomen reopened through previous incision. No fluid or clotted blood present in peritoneal cavity. Stump of corpus uteri brought up and found surrounded by a small clot. No distinct pulsation to be made out in uterine vessels. Well-marked oozing caused by active manipulations of pelvic structures, increased by freshening cut surfaces of previous operation. Closure in layers. Pulse rapid but of good size at end.

Dog No. 10. In excellent condition. Weight 17.5 kilos. March 15th. Ether. Median incision. Uterus very small for so large an animal (has never been pregnant). Uterine vessels cut on both sides. Bleeding by no means so free as in previous cases. Closure in layers. Pulse good at close. 18th. Dog appears as well as before operation.

Dog No. 11. In fairly good condition. Weight about 6 kilos. Considerable enlargement of both thyroids. 18th. Ether. Median incision. Pelvic organs appearing normal.

Uterine vessels of average size; cut on both sides. Bleeding very free. Immediate closure. Pulse rapid but of pretty good volume. 19th. Dog today is bright and playful. Abdomen reopened under ether. One to three drams of bloody fluid found present, and a small blood clot on each broad ligament at site of cut ends of uterine vessel. Removal of clot on right side brought on active arterial hemorrhage. Genital organs now excised in toto, corpus uteri being cut across below level of previous division of uterine vessels. There was profuse bleeding, probably two ounces escaping from abdominal cavity before closure was made. At the end of operation pulse was rapid and of small size. Mucous membranes greatly blanched. Dog able to hold up her head on reaching cage, but making no attempt to rise. 20th. This A.M. dog appears to have recovered well from yesterday's operation. Gets around well. While ether was being administered again dog ceased breathing, and all measures at resuscitation failed. About 6 c.c. of fluid and clotted blood found between bladder and intestines. Intestinal serosa pale.

Dog No. 12. Young bitch, in fairly good condition. Weight 5 kilos. March 21st. Ether. Median incision. Uterus quite small, but vessels of good size for age of dog. Right uterine vessels cut. Free arterial hemorrhage. Immediate closure. Pulse, good volume, not very rapid. 22d. Dog all right today. Under ether, abdomen reopened. 8 to 10 c.c. of bloody fluid and blood clots present. Left uterine vessels were cut, and bled freely. 23d. Dog seems rather weak today, but is able to get around well. Abdomen reopened. About the same amount of blood present as found yesterday. Manipulation of uterus and broad ligaments caused fresh bleeding from uterine vessels. Dog conscious at close. 26th. Dog somewhat dull today. Incision infected and gaping. Killed by forced anesthesia. Several c.c. of purulent fluid found in the pelvis. (Portion of femoral vein removed for study.)

Dog No. 13. In good condition. Weight about 9 kilos. March 25th. Ether. Median incision 5 cm. long. Each oviduct occupied by four fetal sacs, measuring 3.5 x 2.5 cm. Bloodvessels in the broad ligaments dilated, the uterine artery being 2 mm. in diameter at junction of oviduct and corpus uteri. The right vessels were cut at this point. Bleeding was profuse. Immediate closure. At close femoral pulse was just perceptible. Mucous membranes very pale. Seen fifteen minutes later dog lay stretched out, eyes open, breathing quietly; no femoral pulse to be obtained. 26th. Dog appears dull, but drinks freely, and walks around well. Pulse small, 140 per minute. Mucous membranes of better color than yesterday. Given a subcutaneous infusion of salt solution, 200 c.c. 27th. Condition much better. Dog bright. Pulse 104, regular, of fairly good size. Given $\frac{1}{3}$ grain of morphine hypodermically one-half hour before being etherized. Abdomen reopened. Several c.c. of bloody fluid and clots present. Proximal ends of cut uterine vessels closed, but good pulsation still present in artery. The fetal sacs on the left side were brought out, and opened by longitudinal incisions, which were further torn apart with forceps. These tears were made from the distal sac inward on the inferior, the superior, the anterior, and the posterior surfaces of the oviduct, respectively. There was rather free bleeding from one of the torn sacs. Immediate closure. Seen one hour later dog was still prostrated, pulse 120, of fairly good volume. 28th. Dog in excellent spirits today, quite active. Abdomen reopened under ether. A small quantity of fluid and clotted blood present. Some light adhesions about left oviduct. Mucosa of latter everted at sites of previous tears. Good pulsation still present in proximal stump of right uterine artery. Distal portions of the right vessels severed again and the fetal sac adjacent to the corpus uteri on this side torn open. All the left sacs were again cut open in different places, and the left uterine vessel severed. There was the usual free hemorrhage. Dog conscious on reaching bed; pulse very rapid and small. April 2d. Dog rather dull yesterday and today, but gets around well. Has shown no pain. Abdomen reopened for the fourth time this A.M. Several c.c. of dark, bloody fluid present. Bladder much distended: Omentum adherent to fetal sacs. The left uterine vessels were thrombosed in their severed ends. Definite pulsation in the artery could not be made out on either side. The genital organs were now removed, the right ovary being unintentionally left in. The bleeding from the freshly cut uterines and the ovarian as well, was very free. Immediate closure. At end of operation femoral pulse was 140 to 150, irregular and small. Tongue and mucous membranes blanched. One-half hour later given $\frac{1}{4}$ grain of morphine hypodermically. Dog lying with eyes open, but not making any effort to move. Respirations rather shallow but not rapid. A tight binder was placed around the abdomen, and the dog left in Trendelenburg position. Three hours later condition was about the same. Given a subcutaneous infusion of salt solution, 325 c.c. This was promptly taken up, with a slight improvement in the pulse. 3d. Twenty-four hours later dog found in much better condition; able to be on her feet, cheerful, and taking nourishment well. Pulse 120, regular, of fairly good size.

From these few experiments we feel justified more and more in believing that the intra-abdominal hemorrhage, such as we meet with in women in collapse from ruptured ectopic gestation, is not sufficient in itself to cause a fatal termination in these cases.[1]

It will doubtless be maintained by some that our experimental work has shown nothing more than that the dog can withstand a greater loss of blood than the human—a recognized fact—and, yet, it seems to us fair to assume that in five of our experiments we made the tests sufficiently severe to more than equalize the factor of resistance to the loss of blood in the dog, as compared with that of the human being under fairly similar conditions.

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[1] Cases in which the loss of blood *per se* would be sufficient to bring about a fatal termination would seldom be seen in time to save the patient; and it is my firm conviction that in such cases only very rarely (possibly never) is a patient saved by operation. Unfortunately, in not a few of the successful cases reported the details from a pathological standpoint are too meagre to enable us to judge accurately of the exact condition that existed.

In other words, taking into consideration this difference in resistance, by cutting both uterine arteries, and in some instances both ovarians as well, we subjected our dogs to a risk of bleeding to death as great as that incurred by the average woman suffering from a ruptured, tubal pregnancy.

How then shall we explain, to what shall we attribute the fatal ending of so many of the serious cases of ruptured ectopic gestations, and what shall be our treatment?

In our view of these cases, we feel that due consideration must be accorded to other factors than hemorrhage, potent as it may be, that jeopardize the lives of our patients.

Let us recall how, in many of these cases, the attack comes to the patient as a stroke of lightning out of a clear sky, and with its accompanying pain brings to the woman's mind the fear of impending death.

We know so little of what we call "shock," that we cannot estimate it in any definite terms, and yet we feel it must play an important role in rendering the patient's condition so serious, so soon after the onset of the attack and before there is any great loss of blood.

Add to this the moving of the patient from her home to the hospital, the dread of the operation, and, finally, the operation itself, and have we added to, or subtracted from, our patient's chances of recovery?

Whatever we do we must lose some cases, but I believe that our percentage of fatalities will be lower if we refuse to add shock to shock, and rather are satisfied to assist nature to bring about reaction before proceeding to a serious operation.

It gives me great pleasure to acknowledge the valuable help of Dr. M. B. Bonta, the late Resident Gynecologist at the Lakeside Hospital, in the preparation of this paper.

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THE COMPARATIVE ADVANTAGES OF CATGUT AND SILVER-WIRE SUTURES FOR CLOSING THE FASCIA AFTER ABDOMINAL INCISIONS.

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The more common suture materials are silk, catgut, and silkworm gut. No one suture material will suffice for all purposes, although silk can be made available for the majority of cases. Whatever we use, the main point is that it shall be sterile; but, unfortunately, a material that may at first sight appear to be in every way adapted for our purpose, may yet present such apparently insuperable difficulties in the way of rendering it sterile that, in the eyes of the aseptic surgeon, the risks accompanying its use may more than overbalance its other advantages. The material must also be smooth and pliable but not brittle, moderately cheap, and easily obtainable. So far as sterilization is concerned, from bacteriological experiments that we have made with a large number of materials, we would say that they would stand in the following order: (1) Silkworm gut; (2) surgeon's cable twist silk; (3) silver wire; (4) catgut, plain and chromicized. Catgut is in all probability the material that is used more than any other for sutures and ligatures, and it would be an ideal material, but, unfortunately, we have no thoroughly reliable method of rendering it absolutely sterile, without at the same time making it so weak as to unfit it for our purpose. When properly handled, it supports the tissues for a sufficient length of time to allow of a thorough approximation of the parts, and after it has served its purpose the smaller sutures are absorbed. If, then, we could find an absolutely reliable method of sterilizing all sizes of catgut, which did not at the same time destroy its other necessary properties, we should have a ligature material of the highest value. Different specimens of catgut vary greatly, and although some of the methods of sterilization which are advocated are, perhaps, effective in the majority of instances, it not infrequently happens that a few of the inner strands are not rendered sterile, and many cases of suppuration or death, following operations, have been directly traceable to the use of catgut ligatures.

The cumol method, or some of its modifications, of sterilizing catgut must be regarded as probably the most reliable one that we have at the present time. The procedure, however, is somewhat complicated. For some years[1] now we have also been using the plain and chromicized catgut as prepared by Van Horn. On the whole we have found this satisfactory enough when the smaller sizes were used.

In using the large sizes of the chromicized gut, however, we have found that the suture sometimes does not become absorbed, but gradually works its way to the surface of the wound and is then discharged.

We have examined by cultural methods the knots and ends of catgut from wound surfaces, even when the wounds have healed by primary intention, and we have found the catgut teeming with bacteria. In some instances it would seem reasonable to suppose that these bacteria might have produced the unfavorable results that sometimes have taken place in the skin. I have no doubt that chromicized catgut is responsible for many of the immediate, and late superficial and deep, skin infections.

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[1] Since March, 1907, we have been wrapping the glass tubes that contain the catgut in gauze, and boiling them for five minutes just before the operation. Our observations from this standpoint are too recent to draw any reliable deductions, but we feel that by this means we have gained an additional degree of security against infection.

Chromicized catgut has also seemed to me to be responsible for the phlebitis that sometimes takes place in the leg in the so-called clean cases. I have met with a well-marked phlebitis, following an amputation of the cervix, in which chromicized catgut was used.

In order to obtain some idea of the comparative value of chromicized catgut and silver wire in abdominal wounds, as regards immediate or late infections, we have analyzed two series of cases, of 100 each, in which catgut was used in one and silver wire in the other, for bringing the fascia together. The peritoneum and skin in every case was brought together with plain, supposedly sterile catgut. It must be borne in mind that the catgut that was used for the skin might have had something to do with the infections that took place; but this was taken into consideration, and eliminated as far as possible. I find upon inquiry and observation that there is a wide difference among surgeons as to what constitutes an infected wound. I have also observed that when the first dressing of the wound is left to an assistant he may, in his enthusiasm, or to please his chief, almost unconsciously remove the slightest evidences of infection that may have been present. Then, again, the late infections that sometimes occur in the wound are not always brought to the attention of the chief. In this way statistics with reference to the infection of the abdominal wound are not always to be relied upon. I know, from my own experience, how difficult it is, at times, to get the assistants to put down on the records the exact condition of the wound at the first dressing. The infection that may be present may seem so slight that they think the wound should not be considered as being infected, in view of the fact that there is only a slight and temporary evidence of suppuration. My rule is to insist upon an exact description of the condition at the first, and at subsequent dressings. Whenever there is any secretion from the wound, cover-slips are made, and culture tubes are inoculated; and if bacteria, aside from the skin coccus, are present we classify it as an infected wound. If the skin coccus alone is present, with pus, we also call it an infected wound. Unless the secretions from the wound are carefully examined, it is impossible to state that the wound has healed without any infection having been present. I am rather inclined to believe that frequently there is a mild grade of wound infection present in many cases following an abdominal operation, particularly after the so-called clean operations, in which there is a slight but persistent rise of temperature for a few days following the operation. When the skin or superficial edges of the incision are slightly separated, but without the presence of any (macroscopic) secretion, we classify these cases under "slight separation of the incision."

We have made an analysis of 100 abdominal cases in which the deep fascia was brought together with chromicized catgut; and 100 cases in which the fascia was brought together with silver wire. These operations were performed for the usual conditions that the gynecologist meets with.

In the two groups pus was found in the structures that were removed at the time of the operation as follows: seven times in the catgut, and nineteen times in the silver-wire group. In this group the incision showed suppuration in 2 cases in the catgut and 1 in the sliver-wire series. There were also 2 cases in the catgut group which showed some slight separation of the skin, and 1 in the silver-wire group, but without any evidences of suppuration in these latter cases. Consequently, in the original pus cases, with catgut, deep suppuration occurred twice in 7 cases, and with silver wire only once in 19 cases. So far as the immediate results are concerned, the incision was clean and closed in 71 of the catgut, and in 83 of the silver-wire cases. There was a slight separation of the skin edges of the incision in 18 of the catgut, and in 9 of the silver-wire cases.

In the total number in each series of cases the incision showed evidences of infection in 9 of the catgut, and in 3 of the silver-wire cases as follows:

	Chromicized catgut.	Silver wire.
Suppuration of the skin	3	1
Suppuration in superficial fascia	3	0
Suppuration in deep fascia	2	1
Slight serous collection	1	1
Total	9	3

In the adherent cases there were no infections in the deep fascia in either group, but a slight separation of the skin in 10 of the catgut, and 7 of the silver-wire cases; and in 3 cases in the catgut, and 1 in the silver-wire there was a slight suppuration in the skin.

In the non-adherent cases there was suppuration in 3 of the catgut series, and in none of the silver-wire cases.

CONCLUSIONS.

The analysis of the various groups in which chromicized catgut and silver wire, respectively, were used shows that, so far as infection is concerned, the use of silver wire is followed by a less amount of reaction than where chromicized catgut is used, the advantages deducible from this particular series of observations favoring the use of silver wire in the proportion of about 3 to 1. We have also noticed with the chromicized catgut that when suppuration takes place the amount and extent is greater than that met with after the use of silver wire. There can be no doubt but that the immediate results from this standpoint are favorable to the use of silver wire. If, however, the results from the infection with the chromicized catgut are not followed by the occurrence of a hernia, or a further extension of the infection to the peritoneal cavity, it cannot be said that the infection that does occur will produce any serious results in the great majority of instances.

The main objection against the use of silver wire for bringing the fascia together is that one leaves within the wound a substance that may cause the patient some discomfort, because the ends may cause annoyance by sticking into the surrounding tissues. This inconvenience, however, will not often occur if the suture is properly applied, and if the ends are turned over with a thin-jawed pair of hemostatic forceps, so that they form a ball-like end to the suture. It takes a certain amount of practice to adjust them properly, but the analysis of our case shows that we were obliged to remove only 4 sutures in over 400. Whenever such a removal becomes necessary it can easily be performed, without any inconvenience to the patient, by means of an injection of a 2 to 5 per cent. solution of cocaine in the line of incision.

So far as the frequency of hernia is concerned, following the use of chromicized catgut and silver wire, it is difficult to make any definite statements. A priori we would expect it to happen less frequently with the silver wire, as this material undoubtedly will approximate the tissues for a greater length of time than the catgut, and since, moreover, as we have found, the use of the former is less likely to be followed by suppuration of the wound.

So far as our observations go with this particular series of cases there was not a single case in which a hernia was noted. As a matter of fact a separation of the fascia and the muscle does not always take place at once, or in most instances during the first weeks following an abdominal operation; but if these cases should be carefully examined after six months or a year, I feel sure that small and, in some instances, good-sized hernial protrusions would be noticed. I have found this not so infrequently to be the case where I have had to do a secondary operation upon a patient who had been operated upon by another surgeon; and I feel sure that the same criticism could be made in the case of some patients upon whom I have operated. Some years ago we had occasion to examine a considerable number of patients upon whom an abdominal section had been performed, and in a considerable proportion, even where suppuration had not taken place, it was possible to demonstrate a distinct separation of the fascia and muscle between the extremities of the incision. Undoubtedly, some of these areas ultimately become sufficiently enlarged to allow of a hernial bulging in the line of incision. I do not, therefore, believe that one is justified in making the statement that by using any particular sort of suture, or method of approximation, he has ensured against the development of a hernia until he has carefully examined the abdominal wound at least six months or a year after the operation.

PATHOLOGICAL REPORT OF THE GYNECOLOGICAL SERVICE OF THE LAKESIDE HOSPITAL 1901 and 1902.

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In the Pathological Laboratory of the Hospital a room is set aside for the exclusive use of the Gynecological department where all the specimens of tissue removed at operations are taken care of. The room is equipped with all the various reagents and modern appliances which are requisite in the preparation of the specimens, their preservation, and examination.

The work as carried on in the laboratory is of an extensive character owing to the great number of gross specimens obtained and the elaborate detail that is necessary before the finished specimens are laid aside as permanent records fully described and catalogued.

In the years 1901 and 1902—with which this report deals—there were 526 cases which furnished specimens for histological examination. The aim is that all tissues removed at operation shall be subjected to a rigid and careful microscopical examination—the only exceptions to this being the cases in which the tissue is too small in amount for diagnosis. However, this is generally determined with the aid of the microscope as at times a tissue which macroscopically might appear to be wholly insufficient, microscopically is ample in amount. There are some cases, nevertheless, which have furnished too little material for study and definite diagnosis.

The methods employed in the elaboration and completion of the pathological material will be briefly outlined.

All the smaller specimens of tissue removed at operations, such as portions of the endometrium, mucous polypi, cervical tissue, (obtained from a trachelorrhaphy) small pieces of carcinomatous tissue, resected portions for diagnosis etc. are immediately immersed in a 10% solution of formalin in order that as little change as possible may take place in the cells of the tissue.

The larger specimens are placed at once in gauze sponges thoroughly saturated with normal salt solution, to prevent any drying and shrinking before they are taken to the laboratory. After the operations are concluded the specimens are removed to the laboratory. If of sufficient size, they are weighed and their dimensions are accurately taken. A crayon, pen or pencil sketch is made and a gross description of the specimens is recorded, with the name of the patient, the pathologcial number of the case, the date of the operation and its nature.

The large specimens are placed in various solutions for fixation of the tissues—formalin solution, Orth's, Muller's or Zenker's fluid, alcohol etc.—and are allowed to remain until fixation of the cells has been affected and the tissues have been rendered unchangeable. When small portions are cut from the large structures—preferably after hardening—they, with the specimens of endometrium, cervical tissue, etc. are run through alcohol, absolute alcohol, ether and absolute alcohol and celloidin. They are then secured on blocks of wood fibre, each block being numbered. The same numbers are also affixed to the specimens themselves by means of gelatin, acacia or tragacanth, which are insoluble in alcohol. The numbers stick firmly to the specimens for an indefinite time so that when tissues are removed from the blocks, after sections have been cut from them, they are still distinguishable one from the other. These specimens after removal from the blocks are preserved in jars of 50% alcohol, 100 numbers in each container. Thus the original piece of tissue from which the microscopical section is obtained is preserved intact and is always accessible.

As the block specimens are cut from the original gross specimens the site from which the section for examination is taken is marked as closely as possible upon the record sheet and lettered in order to distinguish the various sections of one specimen.

Haemotoxylin—eosin is used except where special conditions warrant the employment of other stains. The time usually employed for the completion of the microscopical slide is approximately two weeks. However, when specimens are desired for examination within a shorter time they can be put through a modification of the above hardening and staining process and finished in from 20 to 24 hours.

The "fresh freezing" process is also used where immediate diagnosis is essential. The stained specimens are mounted in Canada balsam, numbered and laid aside for the histological description and diagnosis, which is afterwards supplied by the resident gynaecologist-in-chief and his assistants.

This part of the work involves much time and labor, as each and every specimen is described in detail, and the diagnosis is made and inscribed on the label on the glass slide before the latter is laid away in the cabinet as a permanent record. The description is written upon special individual sheets, which later are bound into books of a convenient size. Not only is the name index kept but also a disease index so that the record of the pathological diagnosis of any case together with the special pathological lesions found in the tissues may be referred to in an instant.

The systematic and careful pathological examination of all the tissues removed at operation is of incalculable value from the diagnostic and statistical standpoint. From such records we are also able to comprehend with some degree of accuracy lesions of a similar nature occuring in other cases.

Particularly important and interesting are those cases that are seen and studied through the preoperative, operative and post-operative stages, and the determination of the minute or histological lesions as they exist which alone gives us the true insight into the pathological process. Throughout the pathological records it will be noted that very few diagnoses of acute inflammatory conditions are recorded. This is due to the fact that many patients are not admitted until after the acute process has subsided or that the patients with acute lesions are generally allowed to remain at rest under appropriate treatment until their general condition has improved and their temperature practically subsided before radical operative measures are resorted to, so that the process has had time to reach the subacute stage which is generally exemplified in the tissues.

The delay caused by waiting for the acute attack to lessen or to subside may also account in part for the sterility of the purulent exudate found in many of the cases, the bacteria having entirely disappeared or possessing such a low vitality that no cultures grow. The bacteriological factor is studied in conjunction with the pathological lesions. From all infected tissues a culture is made to determine which organism, or organisms are present, their pathogenicity being ascertained by inoculation into animals. Again, the pathological tissue is stained with suitable stains in selected cases to determine if possible the organisms present as for instance the gonococcus, the tubercle bacillus, the streptococcus, actinomyces, etc., and approximately their position and number in the tissues.

The contents of cysts, ascitic fluid, etc are subjected to gravimetric, chemic, histologic and bacteriologic examinations all of which are recorded.

Classification of inflammatory lesions.—In the records dealing with inflammatory processes in the various tissues of the body it seems to be the tendency of many writers not to formulate a simple classification according to the lesions demonstrable but rather to adopt a complex nomenclature. This is true more especially of gynaecological pathological reports.

In many cases in which an apparently large number of glands or in which a mere hyperemia or glandular hypertrophy exists the condition has been designated as inflammation when in reality none existed or probably had never existed. The designation of lesions in the endometrium is no exception and a surfeit of inappropriate terms has been the result. Personally I believe that in-so-far as the true inflammatory reactions are concerned and irrespective of the tissues of the body involved, the two divisions acute and subacute are quite sufficient to describe and indicate the character of the process.

That any inflammation under favorable conditions is always tending towards a healed condition or complete resolution, no matter in what stage it exists, and that the process is really a subacute one throughout after it has passed the transient acute stage cannot be disputed.

The term chronic has been used by us principally for convenience and not because it was essential.

The terms *subacute* and *healed* are preferred to the term *chronic* for the reason that they imply much more. Thus, for instance, when a healed endometritis exists or a healed salpingitis is present there is no more reason for designating it a chronic inflammation then there would be when a cicatrix is present on the hand as the result of an injury. Thus we have deemed it best to use terms which are explicit in themselves and which will convey as plainly as possible the true pathological process.

CLASSIFICATION.

Uterine Lesions.—For the reasons above stated and explained the true inflammatory lesions of the endometrium are included or grouped under the expressive terms:

I Acute endometritis
II Subacute endometritis
III Chronic endometritis

Conditions other than inflammatory are designated under

I Normal endometrium
II Atrophic endometrium
III Healed endometrium
IV Hypertrophy of endometrium
V Glandular dilatation of endometrium
VI Glandular hyperplasia of endometrium

Healed endometrium.—This signifies that many evidences of a preexistent inflammatory reaction are recognizable but that complete healing has occurred, the destructive changes in the tissue alone remaining to differentiate it from the normal.

Hyperaemia of the endometrium may be the result of an inflammatory process which has undergone practically complete resolution or it may result simply from some disturbance with the arterial or venous blood supply, the latter being more frequently the case.

Hypertrophy of the endometrium may also, like hyperemia, be a result of an inflammation in the tissue (or a predisposing factor toward it). Nevertheless, it arises chiefly from the hyperemia present, the latter being essential for the production of the former.

A glandular hypertrophy is not possible without a general hypertrophy of the stroma so that instead of the term glandular hypertrophy, *hypertrophy of the endometrium* has been employed which implies an implication of the tissue, stroma and glands, as a whole in the hypertrophic changes—a condition always seen in the areas where hypertrophy occurs.

Glandular dilatation results generally from an inflammation of the endometrium with destruction of part of the gland epithelium, occlusion of the gland orifice or its partial obliteration to form practically retention cysts of various sizes. It may also result from an atrophy or from pressure changes in the tissue.

Glandular hyperplasia.—The mere presence of numerous glands or the appearance of many glands when the convulated glands are divided several times on the same plane, is not sufficient to warrant a diagnosis of a glandular hyperplasia, as one cannot say that two different specimens of an organ should have exactly the same number of glands. Besides, in most cases the tissue shows no evidences of an inflammatory reaction either present or as having been present.

The writer has seen true hyperplasia of the glands of the endometrium only in subacute inflammations and then only in a few instances. In these cases from the isolated epithelial cells remaining after destruction of the glands, new glands with distinct lumina could be seen in groups originating from the proliferation of these cells. One could not say these would eventually have functionated as glands, perhaps they would have formed retention cysts or so-called glandular dilatations. The increase of glands, then, is but an incident in the inflammatory process and in any subacute inflammation proliferation of the epithelial and connective tissue elements is anticipated in the effort of the tissue to restore its component parts as far as it is possible to do so.

The atrophic group include those specimens of endometrium in which no evidences of a previous inflammatory reaction are recognizable and as the tissue is so uniform in structure it is assumed that the changes present are solely those arising from an atrophic change, whether due to age, ablation of ovaries or other causes.

Diagnosis of specimens of endometrium examined:

Endometritis, Acute	19
Endometritis, Subacute (and chronic)	126
Normal endometrium	54
Atrophic endometrium	4
Healed endometrium	24
Hyperemia of endometrium	91
Glandular hyperplasia of endometrium	3
Hypertrophy of endometrium	103
Glandular dilatation of endometrium	18

Decidual and placental tissues are not included in the above diagnoses. In 21 cases the portions of these tissues examined histologically showed no inflammatory changes and are classed as normal. In three of these cases there was a very small amount of decidual tissue to be seen microscopically in addition to portions of endometrium slightly changed from the normal, chorionic villi being wholly absent. They were, however, considered sufficiently characteristic to be included. 36 cases presented more or less leucocytic infiltration with here and there areas of necrosis of varying size.

Tuerculous endometritis.—In Path No. 659 the endometrium was invaded by a tuberculous process with well formed tubercles containing giant cells; the stroma was infiltrated with round cell leucocytes and here and there were areas of caseation. Partially filling the uterine cavity in this case was a large mucous polyp which presented a marked tuberculous infiltration and constituting a tuberculous mucous polyp. There was also in this case a bilateral tuberculous salpingitis and a general miliary tuberculous peritonitis. A large myoma filled up the pelvis, for which the patient was operated upon—(See myoma and mucous polyps). In the other cases where the endometrium had been recovered and where tuberculous lesions were found in the tubes and ovaries no implication of it was to be made out.

Thrombosis of Vessels in Endometrium.—Path. No. 708 shows a thrombus in a large vessel in the superficial portion of the endometrium which is organized. In structure the thrombus is fairly cellular, shows some hyaline degeneration, is vacuolated here and there, the vacuoles being of small size. The lumen of the vein is entirely occluded while its wall is infiltrated with round-celled leucocytes. Surrounding the whole of the thrombosed vessel is a deep zone of round-celled leucocytes, closely packed.

Some of the arteries of the endometrium show hyaline degeneration of the walls with arteriosclerotic thickening. The endometrium in general shows a chronic endometritis with changes incident thereto such as a diminution in the number of glands, epithelial changes, increased density of the stroma in areas, dilatation of glands, leucocytic (round-celled) infiltration, etc.

Portions of the muscularis obtained with the endometrium from the wall of the uterus present several large thrombosed vessels with the thrombi well organized, and partially or completely occluding the lumina. One large vessel shows a marked proliferation of the cells of the tunica intima, these cells being large and containing large oval nuclei. This thrombus almost obliterates the lumen of the vessel leaving only a small slit-like space at one side which contains red blood cells. The muscularis itself shows degenerative changes in that the tissue stains palely and its nuclei diminished in number. In other thrombi in the muscularis the cells are somewhat flattened and a circular arrangement can be seen. In another thrombus the tissue shows hyaline and granular degeneration and throughout it are many round-celled and plasma-celled leucocytes.

The right tube and ovary removed at operation in this case show a chronic perisalpingitis with a healed salpingitis and a chronic perioophoritis.

The patient (M. H.) from whom this endometrium was obtained died very suddenly on the evening of the day of the operation with all the symptoms of a pulmonary embolus—dyspnoea, cyanosis, frothy exudate from the mouth and nose, weak, rapid pulse, etc. It may be that a thrombus in the wall of the uterus was disturbed sufficiently so that its liberation later caused death.

Case 869, an instance of acute endometritis, showed a polymorphonuclear infiltration not only of the endometrium itself but also a similar leucocytic infiltration of a recent cellular corpus luteum of the ovary which was resected at the operation. The ovarian stroma surrounding the corpus luteum was very slightly infiltrated in a few small areas.

Case 711, an instance of subacute endometritis, resembled a round-celled sacroma to some extent. The tissue was markedly infiltrated with numerous round-celled leucocytes with some eosinophilic cells. There was also an increased vascularity with an almost complete absence of glands.

Adeno-carcinoma corporis uteri occurred twice and in both instances the diagnosis was made from the curettings removed prior to a hysterectomy.

In Path. No. 570 a diffuse involvement of the entire endometrium by the malignant process was to be seen, there being no definite localized area. The tissue had a polypoid appearance. Associated with the adeno-carcinoma was a myomatous condition, the myoma being interstitial but growing inward toward the uterine cavity—in the direction of least resistance. The myoma measured 5.5x4x4 cm. in size and histologically had the typical structure of a fibromyoma.

Path. No. 892 showed macroscopically a nodular growth (2. x 2.5 x 2.5 cm. in diam.) just where the right tube opened into the uterine cavity. The growth had invaded the uterine wall to a depth of one-half its thickness. The conditions revealed in both cases at operation confirmed the diagnosis previously made from the examination of the curettings.

The diagnosis of adeno-carcinoma was readily made after removal of the uterus and the process was seen to have invaded the muscularis. It could, however, be made from an examination of the curetting alone independently of the invasion of the muscularis. Both of these cases have been reported in the American Journal of Obstetrics, Vol. LI, Jan. 1905.

Fibromyomata Uteri.—There were 33 cases in which the uterus showed myomatous involvement, a myomectomy or a hysteromyomectomy being performed.

Path. No. 659 represented the largest myoma removed. It measured 31 x 25 x 17 cm. and was very vascular. Its entire peritoneal surface was closely studded with miliary tubercles. The whole parietal and visceral peritoneum was similarly involved by the tuberculous process.

The fallopian tubes showed miliary tubercles thickly placed over their peritoneal surfaces besides a chronic tuberculous salpingitis. Areas of calcification were to be seen here and there within the tubercles.

A tuberculous endometritis was also present and lying within the distorted uterine cavity was a fair-sized flattened polyp measuring 6 x 4 x 1.5 cm., springing from the endometrium. This polyp showed tuberculous invasion with more or less necrosis (see polyps).

In Path. No. 899 (9) myomata were enucleated from the uterine wall —the uterus itself being saved. These fibromyomatous nodules varied in size, the largest being 12x9x8 cm. and the smallest having a diameter of 2.75 cm. The patient was a nullipara 36 years old.

In Path. No. 570 an adeno-carcinoma was found in addition to the fibromyomatous involvement. (See adeno-carcinoma).

Adeno-myoma uteri was met with in but one instance (Path. No. 556). The patient was a nullipara—48 years old. The tumor showing the adenomatous formation measured 6 x 4.5 x 4 cm. and was pedunculated (subperitoneal). There was also in this case a smaller tumor of typical fibromyomatous structure and devoid of glands.

The adeno-myoma histologically showed about an equal amount of muscle and fibrous connective tissue whose vascularity was fairly good. Adenomatous or gland-like spaces were distributed throughout and were lined by rather high columnar epithelium devoid of cilia. The epithelial cells, one layer in thickness, contained oval, vesicular nuclei and stained uniformly. The lumina of the glands were mostly empty though a few contained blood pigment of a brownish-yellow color and also a few red blood corpuscles.

The gland-like alveoli were arranged in groups and resembled utricular glands. Surrounding these adenomatous spaces there was a loosely arranged stroma which varied in amount in the different areas—in some places being very scanty. The stroma was similar to that of the normal endometrium. In it there was some hemorrhagic infiltration and also a slight infiltration of round-celled leucocytes, these also invading the epithelium of the glands. Some blood pigment was deposited in the stroma about the glands. Von Recklinghausen has been able to establish the fact that these glands open upon the surface of the uterine mucosa and it is conceded that they have their origin from the glands of the uterine mucosa though some consider them Wolffian in origin. When the continuity of the lumina of these glands is disturbed, dilatation of the glands occurs with the formation of retention cysts.

Metritis. This condition was noted in five cases. In two of these it was associated with a myomatous involvement of the uterus and in each case there was a chronic endometritis besides evidences of a bilateral inflammatory reaction in the tubes and ovaries. In neither case was the infiltration extensive in character.

A chronic endometritis was present in two other cases where the muscularis was invaded, the involvement of the latter being secondary to the endometritis.

Path. No. 732, was one of streptococcus infection following a normal labor. Necrotic and suppurative foci were numerous throughout the muscularis, which also showed hyaline, granular and fatty degeneration of the muscle cells. The placenta in this case, some of which had been retained presented the characteristic changes of an acute inflammation as did the muscularis of the uterine wall. A pure culture of streptococcus pyogenes was obtained from the blood and stained, coverslips showed from 1 to 5 cocci within the polymorphonuclear leucocytes besides many which were extracellular. Where two or more cocci lay within the cell they often had an end-to-end or chain-like arrangement.

There were many cases in which tissue from the uterine wall was examined and though the relative amounts of muscle and fibrous tissue would vary a great deal with varying degrees of arteriosclerosis,, vascularity, etc., there was never any evidence that these changes were consequent upon an inflammatory reaction.

Uterine polyps.—In Path. No. 659 a mucous polyp, 6 x 4 x 1.5 cm., almost filled the enlarged and distorted uterine cavity. It sprang from the fundus and was flattened out owing to the compression by the large myomatous mass in the uterine wall. This polyp was infiltrated by a diffuse tuberculous process, many well formed tubercles with giant cells being present. Caseation necrosis had taken place here and there throughout the tissue. The corporeal endometrium also showed a tuberculous involvement.

Cervical polypi.—In five instances polypi which had originated in the cervix were removed. They were of small size and four of them exhibited histologically a similar structure to that of the cervical mucosa. Their structure consisted of a fibrous reticulum containing a varying number of glands lined by high cylindrical epithelium which was continuous with that upon the surface of the polyps.

One polyp (Path. No. 839) represented a cyst, measuring 3 x 2 x 2 cm., whose wall consisted of connective tissue which was of cervical type in structure, rich in vascular supply and 2-3 mm. thick. The interior of the polyp was occupied by two large cystic spaces lined with columnar epithelium with nuclei, at the bases of the cells, of the slender cervical type. The cystic cavities were filled with a bluish-pink homogeneous coagulum.

Small fibromyomata were removed in this case from the uterine wall.

They were typical in structure but showed hyaline degeneration.

Cervicitis.—This diagnosis was made in 48 cases. The tissues presented different degrees of inflammatory reaction, from the acute through the subacute to a chronic stage. In the greater number of cases the specimens of cervical tissue were obtained in the operations of trachelorrhaphy, amputation of the cervix or where a portion was resected for diagnosis.

Erosion of the cervix was noted in one case; a normal cervix was recorded in 6 cases. Glandular dilatation existed in 10 cases, while two cases showed a glandular hypertrophy. The two latter conditions were associated with inflammatory lesions in the cervical tissue.

Adeno-carcinoma of the cervix occurred in one case (Path. No. 752) but was a recurrent process. The patient was 48 years old. She had been operated upon previously on April 13, 1897, when owing to the advanced condition of the disease a curettage with cauterization by the thermocautery was carried out—more radical measures being deemed inadvisable. The patient returned to the hospital again and a second operation of the same nature as the first was performed on Jan. 9, 1902, approximately 4 years and 9 months intervened between the operations during which time the patient had led an active life and enjoyed reasonably good health. A small nodule was resected from the anterior vaginal wall near the urethral tubercle. It was thought it might be a metastatic growth but microscopical examination showed it to be a small multilocular cystic adenoma. (See description under vaginal lesions).

The histological features of the adeno-carcinomatous process were very interesting, in that as the disease advanced and was preceded by a round-celled leucocytic infiltration, healing or healed conditions could be observed in the earlier involved portions of the tissue. The latter areas showed a dense fibrous stroma with relatively little epithelial element, the cells of which were irregular in size, fragmented and varied somewhat in their depth of stain. In some areas only the chromatic remains were present in the stroma to indicate where the epithelial cells had formerly existed.

The general vascularity of the tissue was poor while the stroma was of the usual dense, fibrous variety found in the cervix except for the areas of increased density here and there.

Squamous-celled carcinoma.—There were 13 cases in which this diagnosis was arrived at. In 12 of these cases the clinical diagnosis scarcely required verification histologically as the disease was so far advanced that its nature was self-evident. Path. No. 771 represented a very early case, the process not extending beyond the inner half of the thickness of the cervix which was very slightly enlarged from the normal. A vaginal hysterectomy was carried out in this case.

In one case (Path. No. 955) the involvement of the cervix was secondary to a recurrent primary carcinoma of the vagina. The operative measures carried out in the 13 cases were:

Hysterectomy, 4 cases.
Evacuation of a pyometra, 2 cases,
Curettage and cauterization, 9 cases.

Tubal lesions.—The inflammatory processes within the tube have been classified under the headings of acute, subacute and chronic salpingitis. In none of these was a free purulent exudate present within the lumen of the tube, the inflammatory reaction consisting at the time of the histological examination in the leucocytic infiltration of the various coats along with the other changes in their structure.

The division *pyosalpinx* (acute and subacute) was made to include only those cases in which free pus existed within the lumen of the tube in addition to the infiltration and alteration occurring in the tubal wall.

Another division — *healed salpingitis* — is made to embrace those fallopian tubes which presented all the evidences of a previous inflammatory involvement, but where resolution had progressed to a degree where the structure of the tube approached that of the normal with entire subsidence of the inflammation that had at one time prevailed.

This group form a particularly interesting one in that it shows the changes wrought in a tube by the inflammation once present and how effectually nature has dealt with the condition. In the fallopian tubes of this class many epithelial-lined diverticula are demonstrable. These result from a coalescence of the folds of the mucosa and the inclusion of the epithelial cells which escape destruction during the inflammatory process. New fibrous tissue is developed around these which if formed extensively toward the main lumen of the tube causes these diverticula to be situated far out in the wall of the tube. Some of these epithelial cell inclusions have no communication with the lumen proper of the tube and as the epithelial cells have a secretory function, there being no escape for the fluid formed, retention cysts result. The formation of these false diverticula is generally bilateral owing to the fact that most inflammatory affections of the tubes are bilateral.

With the history of an inflammation usually having preceded the development of an ectopic gestation, a period of previous sterility in many cases, the histological demonstration of an existing inflammation or of a healed salpingitis in not only the tube which lodged the ovum but also in the opposite tube, the constant presence of these false diverticula in which an ovum may lodge and where its further propulsion along the lumen of the tube is impossible a previous salpingitis must be considered as one of the chief causes—if not the chief etiological factor—of the pathological anomaly known as ectopic gestation.

The opposite tube to that which contained the ovum in every case where it was removed and in all the cases of ectopic gestation which have occurred upon the gynaecological service has shown the evidences of an inflammation within the tubes which had preceded the ectopic condition.

Acute salpingitis.—This diagnosis is applied to those cases which show an acute inflammatory reaction but in which the lumen is devoid of a free purulent exudate. There were 5 tubes only which were so involved.

Tubes showing subacute and chronic salpingitis numbered 62.

Pyosalpinx (acute and subacute) 77 tubes in all presented this condition—each tube containing free pus in the lumen in addition to the infiltration of the tube wall. In 26 cases or (52·tubes) there was a bilateral involvement leaving 25 cases in which only one tube was affected. Considering that almost invariably the inflammation is bilateral, the other 25 tubes of those showing a unilateral pyosalpinx presented a healed condition (healed salpingitis) an acute, subacute or chronic salpingitis or in a few cases were seemingly not sufficiently diseased to warrant their removal at the time of operation.

In two cases Streptococcus pyogenes was found, Staphylococcus pyogenes albus in two cases, B. tuberculosis in one case—a pure culture being obtained. In a number of cases gonococci were demonstrable when stained on coverslip but in only one instance was a culture obtained—hydrocele-agar being used as the culture medium.

Tuberculous salpingitis.—Twelve additional cases revealed a tuberculous salpingitis. The process was bilateral in each case. In twelve cases or 50% the lumen of the tube contained puruloid or caseous material, while the remaining 50% presented a chronic tuberculous salpingitis.

The fallopian tube in Path. No. 575 was extremely large being filled with puruloid material of a creamy consistence. It measured 20 cm. long and varied in diameter from 1 cm. to 3.25 cm. From the contents a pure culture of the tubercle bacillus was obtained. Calcification within the tubercles was observed in Path. No. 809 and was bilateral.

Path. No. 576 showed an *ovarian abscess* of small size in either ovary, the right one communicating with a pyosalpinx to form a tubo-ovarian abscess. From the purulent contents of this abscess a pure culture of the colon Bacillus was obtained. This undoubtedly constituted an infection secondary to the tuberculous involvement; not only the tubes but also the ovaries showed an extensive tuberculous process.

Hydrosalpinx occurred in eleven instances; 5 of these were unilateral while 3 were bilateral. None of these were of large size and in each evidences of an inflammatory reaction with occlusion of the os fimbria were present. The condition is secondary usually to an inflammation of the tube with obstruction to the escape of the fluid secreted by the epithelial lining of the tube. Where loculi form from the coalescence of the tubal folds, the fluid accumulating in these and distending them to various degrees gives rise to the so-called follicular hydrosalpinx.

In some of the above cases of hydrosalpinx these cystic loculi of different sizes were present. However, the principal amount of the fluid occupied the distended lumen proper. A chronic salpingitis was present in all of these cases.

Haematosalpinx occurred bilaterally in a single case (Path. No. 763). This pathological affection was undoubtedly due to a haemorrhagic extravasation into the lumina of previously inflamed tubes, the distal extremities of which were occluded. The specimens were of small size.

Tubal pregnancy.—Three cases were found. In all of them rupture had occurred about one month previous to admission according to the history elicited. No foetal remains were to be seen but chorionic villi were demonstrable in each case, some of which were more or less degenerated.

In case No. 996, in the tube which had contained the ovum, a chronic salpingitis was to be seen, while the opposite tube revealed a healed salpingitis. In both fallopian tubes several epithelial loculi had formed from the coalescence of some of the folds of the mucosa. A few of these were dilated or cystic.

Path. No. 874 presented a subacute salpingitis not only in the tube where the ovum lodged but also in the tube of the opposite side. In both fallopian tubes false diverticula formed by the coalescence of the folds of the mucosa were typical—some of them being deeply situated in the muscle wall and being surrounded by new formed connective tissue. In every case of tubal gestation which has occurred on the gynaecological service of the hospital the presence of these false diverticula could be demonstrated. (See remarks under healed salpingitis as to these as causative factors in the production of ectopic tubal gestation). There is no other structural (pathological or congenital) change in the fallopian tubes so constantly present, which could account for the occurrence of this pathological anomaly (tubal pregnancy) except possibly the absence of cilia and the infiltration of the tubal wall, both of which are of themselves insufficient factors.

Normal tubes.— 25 tubes presented no pathological lesions. As many of these were removed during a hysterectomy or hysteromyomectomy a constant pathological lesion was scarcely anticipated.

Tubo-ovarian abscess.—Five cases are on record. In each of these direct communication could be established between the lumen of the tube and the abscess cavity in the ovary.

In Path. No. 576 a previous tuberculous process was demonstrable, both tube and ovary being affected. A pure culture of the colon bacillus was obtained from the contents of this abscess cavity.

Tubo-ovarian cyst.—Path No. 566 presented a follicular hydrosalpinx which communicated with a cyst in the ovary to constitute a tubo-ovarian cyst. The contents of cyst were clear and of a light yellowish color. Changes in the tissues subsequent to an inflammatory reaction were evident in both the tube and ovary.

Perisalpingitic adhesions.—This term is here used instead of the term perisalpingitis for the reason that while these adhesions are the result of an inflammation, in the majority of the cases the inflammation has entirely subsided, all evidences of its activity having vanished, leaving only the connective tissue remnants devoid of leucocytic infiltration and often of little vascularity to indicate a pre-existent inflammation.

In a number of the cases an acute or subacute inflammation existed and this constitutes a true perisalpingitis. The inflammatory process in the tube has been observed in almost all cases to subside from without inward. For convenience of classification the division acute, subacute and chronic is used. There were 179 tubes in all showing perisalpingitic involvement as follows:

Acute perisalpingitis	3
Subacute perisalpingitis	38
Chronic perisalp. adh.	138

Ovarian lesions.—The classification of inflammatory lesions in the ovary has been restricted to acute, subacute and chronic oophoritis. Where pus existed in the ovaries these specimens are included under the heading of ovarian abscess. There are specimens of ovaries which seemingly show healed areas of inflammation. Nevertheless, as these portions of the tissue show so little variation from the normal one cannot always be positive in making a diagnosis of a "healed oophoritis."

Acute oophoritis was found in only two cases. One of these (Path. No. 869) showed an acute infiltration of polymorphonuclear leucocytes into a large recent corpus luteum rich in lutein cells. Part of the ovary containing this corpus luteum was resected. In the ovarian stroma adjacent to the corpus luteum a few small areas of infiltration by polynuclear leucocytes were to be seen. An acute endometritis was present also in this case. (See endometritis).

The fact that we often awaited the subsidence of the acute process as well as the fact that many cases were not admitted until the acute stage had passed accounts for the limited number of "acute diagnoses."

Oophoritis, subacute and chronic, was demonstrable in 42 ovaries. In a number of these cases the diagnoses were made from portions of the ovaries resected at the time of operation. In 7 of the 42 cases, or 16.6% of the cases of subacute and chronic oophoritis, tuberculous lesions were well marked. In those cases where curettage was carried out, no tuberculous lesions were present in the endometrium examined.

In case No. 575 the endometrium showed only a moderate, subacute condition whilst both of the fallopian tubes were markedly involved in the tuberculous process as was also the left ovary. All of these were extirpated—the right ovary being retained.

Ovarian abscess was found in 23 ovaries. Tuberculous lesions were prominent in four of these—no doubt constituting the primary lesion.

From the abscess in case No. 576 the colon bacillus was obtained, although a tuberculous process co-existed.

Path. No. 666 represented a corpus luteum abscess, the corpus luteum alone being resected at operation—the remaining portion of the ovary being saved. In the gross the abscess could be seen limited by the distinct yellow wall of a corpus luteum which was verified by microscopical examination.

Perioophoritic adhesions.—In one case an acute perioophoritis existed, while in 86 cases a subacute or chronic condition was present, two of these showing tuberculous infiltration also. In the acute and subacute cases either a pyosalpinx or an ovarian abscess was found. In the majority of the cases designated as instances of chronic perioophoritis fibrous connective tissue adhesions alone were present and showed no active inflammation—resolution having taken place. These adhesions consisted of bands of various thicknesses enveloping the ovary as a mantle and beneath them the inflammation seldom extended deeply, if at all, into the ovarian substance. In many instances portions of the peritoneal endothelium and germinal epithelium were included beneath these adhesions and the cells were in various stages of preservation. Proliferation of these cells was often seen but showed no definite arrangement. Again these cells formed cystic spaces of various sizes. In places these cells were irregularly scattered throughout the fibrous structure of the bands of adhesions. Again, areas of degeneration with concentric calcification were seen forming the so-called psammoma bodies. In one instance included beneath a band of adhesions was an irregular oval space lined with high columnar epithelium which stained fairly well. These epithelial cells were ciliated, the cilia standing out very distinctly.

Papillary cystoma.—In Path. No. 697 a cyst 5-6 cm. in diameter was removed from the broad ligament, which, however, was slightly adherent to the ovary. The cyst contents were clear with a low specific gravity. The wall of the cyst was quite thin.

Histologically the cyst was lined with low columnar or cuboidal epithelium one layer thick, cilia being absent.

The connective tissue of the wall in its outer part was fibrillated whilst that portion in the papillary processes was myxomatous in type. Vascularity was very poor. This cyst was undoubtedly parovarian in origin.

Path. No. 622 showed a cystic space lined with columnar ciliated epithelium which was reflected over many papillary processes which projected inward. The papillary processes were of connective tissue. The wall was formed mainly of connective tissue of fairly recent origin, but scattered here and there are well defined bundles of unstriped muscle tissue. The tissue of the papillary processes and of the wall in general was densely infiltrated with leucocytes, the polymorphonuclear type predominating. Situated within the more recently formed connective tissue comprising the inner portion of the cyst wall were a number of slit-like spaces devoid of contents or of endothelial lining except in a few which showed a layer of cells detached from the periphery and appearing endothelial-like. Areas of the wall showed necrosis whilst other areas were haemorrhagically infiltrated. Vascularity throughout was good. The contents of the cyst cavity clinging to the wall and between the papillary processes consisted of a bluish stained coagulum containing many polymorphonuclear leucocytes with a few small round cells.

This cyst in reality constituted an abscess but undoubtedly had been secondarily infected. It was a very large one with a wall about 2 cm. thick. Owing to its sessile attachment it was impossible to remove it entirely. A large part of the wall was excised, and the remainder being stitched to the abdominal wall and drainage carried out. About 6 or 8 pints of a very turbid, yellowish-white fluid escaped. It had a strongly urinous odor, coagulated with heat and contained cholesterin crystals. This fluid on microscopic examination showed polymorphonuclear leucocytes corresponding in number to those in the fluid from another abscess cavity. There were also rod-shaped bacilli in fair numbers to be seen. A pure culture of colon bacillus was obtained. The patient made a good recovery.

There were two other cystomata which will also be classified here though from the absence of any epithelial lining or any characteristic structure their exact origin could not be determined. In some respects these two cysts (Path. Nos. 723 and 1000) as well as the papillary cystoma No. 622 above described, were similar in that they were intraligamentous and retroperitoneal and all contained cholesterin crystals, these being present also in the cyst wall as evidenced by the clear spaces remaining —the crystals having dissolved out in the preparation of the specimens.

In Path. No. 622 described above under papillary cystoma, the cyst had a very thick wall (2 cm.), and here and there toward the inner wall of cyst, which consisted of richly cellular connective tissue, were slit-like spaces which had evidently contained cholesterin crystals. In one or two only of these spaces were any cells present and these appeared to be of connective-tissue origin arising from the surrounding tissue.

In Path. No. 723 the cyst wall was about 5 cm. in thickness and was devoid of any epithelial lining. No muscle tissue was present. Many slit-like spaces of different sizes, devoid of an endothelial lining were scattered throughout a fairly thick, somewhat cellular zone of connective tissue. At the periphery of these spaces, either completely surrounding them or at one side, are protoplasmic masses which take a bluish stain with haematoxylin and contain varying numbers of oval or spherical nuclei which stain deeply. In some cases these cells are but one layer thick surrounding the clear space, but again they appear as multinucleated giant cells, which the clear area subdivides. These cells have developed from the connective tissue and are due in all probability to the cholesterin crystals which act as a foreign body. The fluid contents of the cyst was only slightly cloudy but contained many cholesterin crystals.

Path. No. 1000, like Path. No. 622, showed a thick-walled intraligamentary sessile cystoma whose contents were of a yellowish colored fluid containing cholesterin crystals. It was impossible to remove the whole of the cyst owing to its sessile attachment. The lower remaining portion was attached to the tissue around the abdominal incision and drainage was carried out—the patient made a good recovery.

In the wall of this cyst similar protoplasmic masses, quite numerous, surrounding clear slit-like spaces, as in Path. No. 723, were present. The tissue comprising the wall was mainly connective tissue, that nearest the cyst cavity being richly cellular and in this layer the cholesterin crystals were all deposited. There were areas showing myxomatous degeneration, whilst throughout were well formed bundles of unstriped muscle tissue. The connective tissue as a whole showed more or less hyaline degeneration and its vascularity was poor. Around some of the large vessels there was a round celled infiltration.

Papillary adeno-cystoma.—Path. No. 544 presented a cyst 3.5 x 3.5 x 2.5 cm. in size. It was unilocular and was attached to the outer pole of the ovary from which it was resected. It was but lightly adherent to the ovary and evidently had its origin in the broad ligament and was of parovarian origin. A clear yellowish fluid of light specific gravity filled the cyst.

Histologically the cyst was lined with columnar ciliated epithelium which was reflected over the papillary processes. The epithelium was largely one cell in thickness but in some places showed several layers due to an inflammatory proliferation. There were no evidences of a malignant change in the epithelium.

Gland-like or adenomatous spaces, few in number throughout the wall were lined by similar epithelium. The epithelium in places was absent or undergoing degenerative changes. The tissue of the cyst wall outside of the epithelial elements was of the ordinary connective-tissue type in which no muscle tissue could be seen. Here and there the papillary processes had adhered and enclosed epithelial cells which showed slight proliferative changes. The connective tissue of the papillary processes was densely infiltrated by round celled leucocytes, whilst the tissue of the wall without this was only moderately infiltrated. The cyst wall in areas was necrotic.

Multilocular adenocystcarcinoma was met with in one case.—Path. No. 1016. Both ovaries were involved though the tumor on the left side was much smaller than that on the right, the former measuring 8.5 x 8 x 8 cm., the latter 27 x 13 x 9 cm.

The surface of each cyst was irregular or bossed, due to the protruding daughter cysts. Here and there umbilications were to be seen involving areas as large as 5 cm. in diameter and beneath these areas marked resistance was noted on palpation, indicative of growths within the daughter cysts at these points. The umbilications were undoubtedly due to a contraction of the fibrous-tissue trabeculae which supported the clusters of daughter cysts or glands beneath.

On section of the cysts no papillary processes were to be seen, the masses being composed of innumerable cystic spaces from some very minute and just visible to others fairly large. All contained a brownish translucent coagulum. There was no distinct central cavity in the tumor mass. The glands and cystic spaces were lined with columnar epithelium one or more layers in thickness devoid of cilia. New glands could be seen in process of formation from the proliferated epithelium within the glandular and cystic spaces, as also from the masses of proliferated epithelium here and there in the stroma. Large areas presented typical ovarian stroma in which no Graafian follicles were discoverable; areas of necrosis were seen here and there. There was metastatic involvement of the mesentery from which a small nodule, 1 x 1 x .3 cm. was removed for histological purposes.

Multilocular papillary adeno-cysto-carcinoma.—Path. No. 766 showed a bilateral involvement but the case proved to be an inoperable one. The abdomen was opened and the cysts which were multilocular had a sessile and broad attachment in the pelvis. In addition there were metastatic growths in the mesentery and omentum, one of which measuring 4.5 x 2.25 x 3 cm. was removed. There was considerable sanguino-serous ascitic fluid free in the peritoneal cavity. The diagnosis in this case was made from the microscopic appearance of the tumors as well as from the histological character of the nodule removed from the omentum. The small glandulo-cystic spaces were lined with columnar epithelium without cilia, which was reflected over many small papillary processes which projected inward. The epithelium was one or more layers thick and here and there masses of epithelium were seen, new glands being in process of formation from them. A few karyokinetic figures were to be seen.

Dermoid cyst (*multilocular*) Path. No. 823 showed a moderately large dermoid cyst which was removed per vaginam after evacuation of the sac which measured 12-13 cm. in diameter. The fluid (400 cc.) which escaped contained sebaceous material, cholesterin crystals, mucin, etc.

At one side of the large cystic space were several small cystic cavities, on opening which a thick glairy, mucinous fluid escaped. In addition to normal ovarian stroma the cyst wall showed bundles of striped muscle, numerous hairs springing from the inner surface of the cyst wall, spicules of bone, sudoriparous and sebaceous glands, tissue corresponding to that of a spinal ganglion, to that of the large intestine and to that of the fallopian tube. There was also lymphoid, fatty and fibrous connective tissue. The patient in this case was 32 years of age, had borne five children, the last three years previous to the operation. The chief symptoms complained of were menorrhagia with slight dysmenorrhoea, dragging and bearing-down pains in the pelvis especially upon the left side, persistent vomiting for the previous two or three weeks, and constipation.

Corpus luteum cysts.—In 20 cases this diagnosis was recorded. In no instance were the cysts of large size. In several lutein cells could be seen in some part of their wall, and in other cases the cyst had developed in the so-called corpus fibrosum, its wall then consisting of a band of connective tissue which varied in structure from one that was rich in nuclei to one completely hyaline. The walls of some of these cysts showed deposits of blood pigment besides a haemorrhagic and a mild leucocytic infiltration. The contents of the cysts consisted sometimes of a clear fluid devoid of cellular elements. Again, a cyst would contain a haemorrhagic fluid with a few or a moderate number of leucocytes.

The ovary is seldom removed for this condition; the cyst being resected. In the majority of these cases the ovary has been extirpated for some other pathological lesion.

Parovarian cysts.—These were met with in nine instances, but the cysts were all of small size the largest measuring 8 cm. in diameter (Path. No. 778). In the wall of this cyst a psammoma was present.

Path. No. 544 described under papillary adeno-cystoma showed a parovarian cyst.

In Path. No. 697 the growth classified under papillary cystoma was also parovarian in origin.

In Path. No. 622 and 1000 it is difficult to ascertain their true origin.

In the latter the epithelial lining was wholly absent whilst in the former it gave no definite clue as to the structure in which it had developed. In the wall of each well formed bundles of muscle tissue were present and cholesterin crystals occupied slit-like spaces within a new formed zone of connective tissue. The fluid contents of each cyst contained cholesterin crystals. In each case the cyst was intraligamentary and in its growth extended upward retroperitoneally. The two latter cysts are described under the heading papillary cystoma.

Normal ovaries.—In 70 ovaries examined the diagnosis of a normal condition was made. This number does not signify that as many entire ovaries were removed as there were diagnoses because in most of the cases a resection of one or both ovaries was resorted to as a conservative measure. In some a perioophoritis was present in the gross specimen, yet in the microscopic section the delicate adhesion was not in evidence and to all appearances the ovary was normal.

Vagina.—Primary squamous-celled carcinoma was met with in one case (Path. No. 846). The disease was in an advanced stage and involved the left wall of the vagina. The growth extended upward to within 1½-2 cm. of the cervix uteri. Palliative measures only were carried out—curettage with cauterization. The patient had a second similar operation later for a recurrence.

The histological appearance was that of a typical squamous-celled carcinoma. The patient was 47 years old and had been married 16 years. She had given birth to 8 children, the youngest having been born three months previous to her admission. The symptoms she complained of were a tumor in the vagina, haemorrhages, pain in the hips and lower end of the spine, backache, loss of weight, malaise, etc., attacks of diarrhoea alternating with constipation.

Vaginal cysts.—Path. No. 535 showed a small glandulo-cystic nodule which was excised from the anterior vaginal wall near the site of the urethral tubercle. It was 1.5 cm. in diameter. Its external surface was covered with a layer of stratified squamous epithelium varying in thickness. Beneath this and also surrounding the cystic portion was a fibrous tissue wall 3-4 mm. thick, quite vascular and infiltrated in areas by small round celled leucocytes in fair numbers.

The cystic space was lined by high cylindrical epithelium similar to that seen in the cervical glands and devoid of cilia. The nuclei of these cells were slender. The protoplasm of the cells stained bluish. Although there was also an adeno-carcinoma of cervix uteri present in this case, this specimen did not represent a metastatic implantation.

Path. No. 693 represented a very small inclusion cyst developing from the squamous epithelium. It was almost devoid of epithelial lining.

Vulva-Condyloma simplex.—Three instances were recorded. In each instance the usual papillary character of the growth was to be seen with here and there superficial areas showing an inflammatory reaction with leucocytic infiltration, etc.

In one case the labium majus was excised in part for an extensive varicose enlargement. The histological appearances were unimportant.

Urethra.—One case presented a syphilitic ulcer, the tissue of which histologically showed a dense leucocytic infiltration of round-celled and polymorphonuclear leucocytes, but nothing characteristic of its syphilitic nature. The history of the case with the rapid disappearance of the process under antisyphilitic treatment established the diagnosis.

The diagnosis of urethral caruncle was made in one case—Path. No. 814. The growth was small and presented the usual histological appearance.

Breast.—In conjunction with other operative procedures a tumor was removed from the mammary gland in three cases. The tumors were circumscribed and in each case had the typical histological structure of an adeno-fibroma.

Appendix.—In the routine examination of this organ which is carried out at the time of operation, it was found sufficiently involved to be removed in 139 cases. Upon histological examination the following diagnoses were recorded:

Normal appendix.—In 53 specimens a normal condition was present although removal was indicated from the macroscopical appearance at the time of the operation. Flexions were present in some, adhesions upon themselves and to the mesentery, etc. in others, while some appeared more or less hypertrophied or dilated.

Dilated appendix.—This condition was found in 22 specimens. It was generally due to an acute flexion with some constriction, to a constriction alone or to a concretion within.

Concretions were found within the lumen of the appendix in six cases. These were composed of concentrically formed masses of hardened faecal debris with more or less cellular detritus from the inner layers of the wall of the appendix, leucocytes, red blood cells, etc.

Appendicitis acuta was well marked in two cases. In Path. No. 605 the patient was 12 years old and was operated upon for the appendiceal condition alone. In the other case (Path. No. 624) the condition of the appendix had never been suspected, the patient being operated upon for a retroversion of the uterus, lacerated cervix and perineum.

The wall of the appendix was densely infiltrated with polymorphonuclear leucocytes and upon one side was quite necrotic, a fair sized flake of lymph which lacked any organization being attached to the surface over this area.

Appendicitis subacuta was noted in two cases.

Appendicitis chronica. In 22 cases this condition was recorded while in 22 other cases the condition of appendicitis obliterans (so-called) was found. In a number of the latter a total occlusion existed, while in the remainder changes incident toward the development of an occlusion were taking place such as the destruction and obliteration of the mucosa and its glands with a diminished size of the lumen, etc.

Appendix with Ova of the Ascaris Lumbricoides.—This condition was found in one instance (Path. No. 632) in an appendix which otherwise was normal in structure except for a mild chronic periappendicitis. Within the lumen, suspended by a small amount of detritus and also free were to be seen the well developed eggs. No fewer than 6 ova were to be seen in any part of the lumen and this number varied up to as high as 21. An ovum was seen in a gland of the mucosa in two instances. The appendix was 6.5 cm. in length and 4-6 mm. in diameter. Exclusive of a few chronic adhesions and the presence in the lumen of the ova it was normal.

Periappendicitis acuta was found in two cases.

Periappendicitis subacuta was found in eight cases.

Periappendicitis chronica was found in twelve cases.

In one of the chronic cases an area of calcification (psammoma) was present, being situated superficially.

Omentum.—In five cases no pathological changes were evident microscopially in the tissues examined.

Omentitis acuta was observed in eight cases.

Omentitis subacuta was observed in seven cases.

Omentitis chronica was observed in four cases.

These were all secondary to inflammatory lesions elsewhere, constituting adhesions. In Path. No. 596 there was a tuberculous omentitis which was most likely secondary to a bilateral caseous tuberculous salpingitis. The omentum was very thick and a small portion only removed for histological examination.

The following diagnoses were also recorded:

Lipoma, one case.

Sebaceous cyst, three cases.

Ulcerated haemorrhoid, one case.

Thrombosed ext. haemorrhoid (organized), one case.

Abdominal cicatrix, four cases—in one of these the tissue from the abdominal scar contained a number of giant cells presumably due to the irritation caused by a ligature. However, in the omentum of this case which showed an acute inflammation and which was not adherent to the abdominal cicatrix exactly the same type of giant cells were seen.

Adenitis acuta, one case.

Adenitis subacuta, one case.

Necrotic abscess wall (from vaginal puncture), one case.

Tuberculous tissue from abscess wall (from vaginal puncture), 1 case.

Sinus wall (abdominal) subacute inflammation, one case.

REPORT IN GYNECOLOGICAL PATHOLOGY.

BY HOWARD DITTRICK, M. B., LATE RESIDENT GYNECOLOGIST TO THE LAKESIDE HOSPITAL.

In this paper it is my intention to record the varying pathological conditions that were met with during two years' service in the Gynecological Department of Lakeside Hospital and to draw attention to the more instructive features.

It is the practice in this clinic to send to the laboratory all tissues removed at operation. There a gross description with drawings is made. The tissues are then hardened and later examined under the microscope. All the protocols of the findings are finally bound in volumes and form a part of the hospital records.

Workers in this branch of medical science have to contend with a large amount of routine but the compensation that comes when unsuspected cases of tuberculosis or carcinoma are discovered fully repays one for all his trouble. The more interesting cases that are here recorded were not recognized until the slides were examined microscopically. For example, a large pyosalpinx removed from a patient on macroscopic examination showed in the cavity areas which resembled granulation tissue. How much labor would have been saved had this been labelled an ordinary pus tube as it then appeared to be. What satisfaction, however, this finding afforded us, and how well it fitted in with the clinical symptoms when we demonstrated in the anterior of this sac chorionic villi, from which we could affirm positively that we were dealing with a case of infected tubal pregnancy. Again, how valuable are the results of many findings from a prognostic standpoint more especially in malignant disease! The specimens that were examined during this period were obtained from 552 cases from the service of Dr. Hunter Robb and to his encouragement I am largely indebted for the many valuable lessons I have learned in the study of the pathology of the female generative organs.

The various conditions will be taken up when considering the organs which they involved.

Uterus: In 138 cases the endometrium was normal. The inflammatory conditions could be divided into the acute and chronic forms. There were 7 cases of acute endometritis, one of which was associated with a large pelvic abscess and the remainder of which were due to infections following labor or miscarriage. There were 119 cases of chronic endometritis, but in only 19 or 3½% of the 552 cases was the process well marked. There was one case of so-called "senile" inflammation. Another case showed areas of an acute exacerbation of an old chronic process. In another case large numbers of eosinophiles were seen. In only one case was the infiltration distinctly periglandular, a fact that supported strongly the above classification of these inflammations rather than the subdivision into glandular and interstitial varieties.

There were 62 cases of glandular hypertrophy and in only 9 were these associated with a co-existing chronic endometritis (another argument in favor of the above classification of inflammations of the endometrium). In 11 of the 62 cases there was a marked increase in the gland tissue, the remainder showing only a moderate hypertrophy. One case also showed marked glandular dilatation.

The condition usually designated as an oedema of the endometrium due to interference with the blood supply, as in cases of retroversion or fibroid tumors, was met with in 30 cases. In 3 cases the mucous membrane presented marked knoblike excrescences and was termed a polypoid endomertium. In 3 cases there was a marked hypertrophy of the mucosa and in one of these it was expelled as a cast of the uterus. This occurred in a virgin and the specimen was about the size and shape of the normal uterus and microscopically the appearance was that of normal endometrium.

There were 6 cases of tuberculosis of the endometrium, all of which were discovered accidentally through the routine examination of curettings.

There were 13 cases of normal cervix, 15 of chronic cervicitis and 2 of true cervical erosion.

Placental tissue was obtained in 21 cases, 7 of which were normal, 13 infected, and 1 syphilitic.

The last case was that of a colored woman of 21 years, who gave no other luetic history than the occurrence of 5 miscarriages. The placenta was adherent and even in the gross specimens the villi were seen to be thickened and knoblike.

There were 30 cases in which decidual tissue was met with and in 24 of these there had been an acute infection.

Polypi were encountered in 10 cases. Three of these had arisen from the fundus and 7 from the cervix. In one of the latter the sides of the polypi were covered by a layer of columnar epithelium, while the tip was covered by stratified epithelium.

In sections of the muscular wall there were 14 normal cases and the following pathological conditions; acute metritis in 2 cases, one being a case of infection after an induced abortion with the formation of miliary abscesses; chronic metritis in 1 case associated with a carcinoma of the cervix; abscess of the uterine wall in 2 cases; one of which had followed an excision of a myoma from the anterior wall; tuberculosis in 1 case evidenced by a caseous area the size of a bean; atrophic uterus in 1 case; subinvolution alone in 3 cases.

Myomata were found in 33 cases (6%). They were distributed as follows: 3 submucous, 27 interstitial and 13 subserous. In 5 cases there was marked hyaline degeneration and in an additional case cystic changes had occurred. In none of these cases were sarcomatous changes met with.

Adenomyomata were present in three cases. One case showed a diffuse growth throughout the entire muscular wall; in the second there was an interstitial nodule the size of a golf ball; in the third were two encapsulated nodules the size of marbles at either uterine cornu.

The malignant growths also were interesting and occurred in 22 cases (4%) divided as follows:

Carcinoma of the cervix squamous celled	15 cases.
Adenocarcinoma of the cervix	2 cases.
Adenocarcinoma of the fundus	3 cases.
Squamous celled carcinoma of cervical polyp, also invading the cervix	2 cases.
Sarcocarcinoma of a cervical polyp	1 case.

In one of the cases of squamous celled carcinoma of the cervix a metastasis was found in an iliac gland. In one of the cases of cancer of the fundus the patient was operated upon for a pelvic abscess. Curettement was carried out as a routine measure and on examination under the microscopic the above condition was found. The last three cases in the list also emphasize a danger from polypi which is very often not considered, namely their liability to become malignant. In the last case the epithelial covering had undergone a carcinomatous change while the stroma was the seat of a marked sarcomatous degeneration. In 5 cases, the tissue obtained by curettage was too scanty for diagnosis.

Vulva: Very few pathological conditions of this region were seen and the majority were only incidental to other changes within the pelvis. Condyloma simplex occurred in 3 cases. A benign ulcer was found in 2 cases. A sebaceous cyst, the size of a walnut was attached by a pedicle to the labium minus in one case. A small fibroma, 1 cm. in diameter was found in the labium majus in one patient. In one case a specimen of urethral caruncle was found.

Epithelioma of the vulva was met with in 3 cases. From one of these specimens were obtained on four different occasions and finally at autopsy metastases were found along the deep inguinal and iliac arteries. Metastatic nodules were also found in the bladder, stomach, both lungs, left pleura and the heart. In the second case, there was involvement of the inguinal glands on both sides when the patient first came under observation. In the third case metastases in the inguinal glands of the same side were removed seven months after the original tumor had been excised and presented a typical picture of epithelioma under the microscope. These cases were reported in detail in the American Journal of the Medical Sciences, August, 1905.

Vagina: In a few cases tissue was obtained from this region. In four instances there was nothing abnormal. There were four cases of chronic vaginitis. One of these was due to irritation from wearing a pessary which had given rise to many papillary excrescences at the point of pressure. One instance of vaginal cyst was found. This was a retention cyst filled with brownish sebaceous material. In another specimen a vaginal cicatrix was found. In one instance a thin white cast of the vagina was observed after the use of a strong irritant to the mucosa. There was one case of squamous celled carcinoma of the vagina occurring as a metastasis from a similar growth in the cervix six months after hysterectomy. In two cases of vaginal puncture tissue was obtained which was too scanty for diagnosis. In an additional case tissue from a vesico-vaginal fistula was examined which showed no unusual features.

Ovary: A normal ovary was found in 16 cases, and in 3 of these cases this was the condition of both sides. In one of these cases a calcareous nodule was found in the cortex. In an additional case a pea-sized pedunculated outgrowth of normal ovarian tissue was found on the surface. In one case both ovaries were atrophic, each being about the size of a Lima bean and made up entirely of a very dense fibrous tissue. These normal ovaries were removed mainly in cases of fibroid or cancerous disease of the uterus.

Although the specimens examined in connection with this paper were obtained from patients, a large percentage of whom were afflicted with pelvic inflammatory disease, it is remarkable to find the comparatively small number of cases of inflammation of the ovary.

There were in this series 163 cases of tubal inflammation, while a similar process was found in the ovary as follows: Perioophoritis in 61 cases, chronic oophoritis in 13 cases and abscess in 26 cases. Thus it will be seen that in only 39 of 163 cases of tubal disease was there an inflammatory reaction within the ovary, while in all the cases there were adhesions about the ovary. In only the worst cases was the ovary removed, but could every ovary be examined in which the tube is diseased, the ratio would prove to be much smaller than that given above.

The infection does not invade the ovary because of the dense resistant tunica albuginea and when the adhesions are wiped off, the organ can be safely left in situ. This fact has been of great assistance to modern surgeons who advocate the conservative treatment of the ovary.

The 61 cases of perioophoritis include only those without any other pathological condition of the ovary and where adhesions on the surface were due to ovarian abscess or oophoritis the latter diagnoses were made. In one case of perioophoritis, psammoma bodies were found immediately beneath the adhesion. In 3 of the abscess cases, both sides were similarly involved.

Tuberculosis was met with in two cases, one being of the miliary variety involving the peritoneum, while in the other there was abscess formation.

In regard to the corpus luteum the following conditions were found. Normal in 25; free in peritoneal cavity in 1 case; chronic inflammation in 1 case; corpus luteum of pregnancy in 1 case; corpus luteum cyst in 19 cases.

Hypertrophy of the Graafian follicles was found in 38 cases. In two of them both sides were involved, and in 5 cases the follicles were so much enlarged that they formed definite cysts of the ovary.

Cysts: The classification of ovarian cystomata may be based either upon origin or structure. The former is the more difficult, for when a cyst has attained a large size and distorted the broad ligament by its increase in size, it is, in advanced cases, almost impossible to be sure of its origin.

In addition to the 19 cases of corpus luteum cysts and 5 cases of hypertrophy of Graafian follicles so large that they formed cystic tumors the following varieties of cystic disease were encountered:

Simple unilocular cysts in 5 cases.
Simple multilocular cysts in 2 cases.
Adenocystoma in 2 cases.
Papillary cystoma in 3 cases.
Papillary adenocystoma in 1 case.
Papillary cystoadenocarcinoma in 2 cases.
Parovarian cysts (small) in 11 cases.
Dermoid cyst in 1 case.

In the simple unilocular cysts the lining epithelium had become altered by pressure to such an extent that it was impossible to tell the origin. The greater number probably had formed from a Graafian follicle. In one of these cases the cystic cavity in the ovary was continuous with the lumen of the fallopian tube forming a so-called tubo-ovarian cyst.

Of the two multilocular cysts one measured 3 x 2 x 1.5 cm; the larger one was filled with 6500 cc. of fluid. The smaller cyst contained a thick colloid material; in the larger one the fluid was straw colored, rich in albumin, and contained many cholesterin crystals. In both cases the epithelial lining was identical, the cells being of the high cylindrical type, many of them goblet-shaped.

The two cases of adenocystoma were characterized by the appearance of many dilated gland spaces, varying in size, in the cortex of the ovary and lined by epithelium which was not quite as high as in the preceding variety.

Of the three papillary cystomata only one case was bilateral. The first case was an early one in which the cyst was filled with a colloid material. The epithelium was low cuboidal in type and there were a few simple papillae extending into the lumen. The second tumor contained 2500 cc. of yellowish brown fluid with a thick deposit of coagulated fibrin about the anterior of the wall. Within the tumor there were three large cysts, with a smooth lining, opening into each other, with a secondary firm mass made up of cystic spaces filled with papillary processes. The third case was even more interesting. The disease was bilateral. The larger cyst 12 x 6 x 6 cm. was unilocular and papillae were seen scattered over the inner wall. On the peritoneal surface of the opposite ovary a few small papillary masses were observed while a similar unilocular cyst was found in the centre of the ovary. In both of the last tumors areas of old hemorrhage were seen in the wall.

One specimen of the papillary adenocystoma contained 4000 cc. of fluid resembling thin pea soup. There was some degeneration of the papillae and it was doubtful whether or not this was malignant. After four years, however, there has been no recurrence. The two malignant cases were in patients who were markedly emaciated. In the first case there was present a multilocular tumor showing portions which were quite firm. It contained 1500 cc. of clear amber colloid-like fluid. Papillae were seen on the inner surface of all the cysts. The firmer portion of the tumor was made up of almost solid masses of glands with little or no connective tissue stroma. The epithelium showed rapid proliferation as evidenced by the presence of numerous regular and irregular mitotic figures. There was also considerable necrosis throughout these epithelial masses. The other case was even more instructive. At the time of operation free fluid in the abdomen was encountered and the entire peritoneum was studded with grey tubercles. A cyst was removed from the left side while from the right was obtained a mass of nodules which on section showed in the centre degeneration very similar to caseation in tuberculous glands. At that time it was thought that the case was one of tuberculosis. The microscope revealed the fact that the condition in reality was that of bilateral papillary cystoadenocarcinoma. The cyst on the right side had ruptured and given rise to a condition of miliary carcinosis of the peritoneum. On microscopical examination there could be seen in each of the tubercles an area of adenocarcinoma. Metastases were found in the specimens which were removed from both tubes and the appendix.

The parovarian cysts were small and arose from the parovarian body and showed nothing of special interest. Small gritty particles known as psammomata were found in one simple multilocular cyst—one papillary cystoma—one adenocystoma, one papillary adenocystoma and one of the malignant cysts.

There was one instance of a dermoid cyst about the size of a golf ball which microscopically showed the presence of sweat glands, sebaceous glands, lung tissue, giant cells and hair follicles.

Of the solid tumors of the ovary but one form was seen. The case was one of fibroma of the ovary. It was a firm hard tumor the size of a grape fruit made up of a dense fibrous tissue with many areas of cystic degeneration. The tissues were very much altered in appearance on account of a twist in the pedicle.

In another instance a hematoma of the ovary was found. The border of this mass was so changed that the etiology of the tumor was difficult to determine.

One interesting feature of the tumors of the ovary was a twist of the pedicle in three cases. In one case of a simple unilocular cyst, the size of a cocoanut, the whole tumor was dark in color and hemorrhage had occurred into the cyst wall. The second case was that of a multilocular papillary cystoma containing 2500 c. c. of fluid, in which there had been hemorrhage into the pedicle and into the wall of the tumor. The last case was one of fibroma of the ovary in which the tumor was partially necrotic with accompanying widespread peritonitis. In this instance besides hemorrhage into the tumor and the pedicle there was a well-marked hematosalpinx.

The malignant tumors of the ovary were limited to the two cases of papillary cystoadenocarcinoma previously mentioned.

Tube: A normal condition was found in 39 cases in 10 of which both sides were normal.

Inflammatory changes were frequent and the study of the cells in these conditions is very instructive. In addition to the ordinary lymphocytes and polymorphonuclear leucocytes one finds, especially in the acute cases, plasma cells and eosinophiles. The latter are very numerous in pus cases. It is not unusual to find at least 60 eosinophiles in a single field under the high power. In chronic cases degenerative changes of the epithelium may give rise to psammoma bodies.

The inflammations and allied conditions of the tube were divided as follows:

Perisalpingitis in 28 cases, 4 of which were bilateral.
Acute salpingitis in 2 cases.
Chronic salpingitis in 75 cases, 30 of which were bilateral.
Pyosalpinx in 57 cases, 32 of which were bilateral.
Hydrosalpinx simplex in 22 cases, 5 of which were bilateral.
Hydrosalpinx follicularis in 6 cases, 1 of which was bilateral.
Hematosalpinx in 9 cases.

The cases of perisalpingitis were those in which this was the only pathological feature present in the tube and does not include cases of pus tubes in which adhesions were noted.

Among the cases of chronic salpingitis was one in which small nodules had formed throughout the tube—a condition termed by some authorities salpingitis nodosa.

There were three unusual cases of pyosalpinx. In two of these the abscess cavity was found in the muscular wall, while the mucosa showed very little pathological change. In the third case pus was not detected macroscopically but was only revealed on microscopic examination.

There was one case of acute inflammation of a simple hydrosalpinx.

The cases of hematosalpinx were due to tubal pregnancy, twisted pedicle in ovarian tumors, recent inflammation, or undetermined causes.

Tuberculosis of the tube was present in 11 cases. In one case this was only a part of the general miliary involvement of the peritoneum. In all the cases save one the disease was bilateral and in this exception although one tube only was removed by vaginal incision the opposite side in all probability was affected.

Tubal pregnancy was present in six cases.

There were only 5 cases of tumor formation in the tube. Among this number were 4 marked cases of hydatids of Morgagni. The other case was one of metastases in both tubes from a papillary cystoadenocarcinoma which was primary in the ovary.

APPENDIX.

From these 552 cases there were specimens of the appendix obtained in 156 cases and the condition of the organ was as follows:

1. Normal in .... 57 cases or 36.5%
2. Chronic appendicitis in .... 40 cases or 25.5%
3. Periappendicitis in .... 31 cases or 20 %
4. Occluded appendix in .... 17 cases or 11 %
5. Concretions in the appendix in ...... 7 cases or 45 %
6. Other conditions—
    (a) Metastasis from a papillary cystoadenocarcinoma of the ovary, ... 1 case
    (b) Tuberculosis .... 1 case
    (c) Polyp of mucosa .... 1 case
    (d) Dilated appendix .... 1 case

4 cases or 2.5%

It is a striking feature that out of 156 patients who were not operated upon primarily for disease of this organ, 99 cases or 63% should have shown a pathological condition in the appendix.

Broad Ligament: There was one interesting specimen of adenomyoma of the broad ligament in a case in which there was also an adenomyoma of the uterus and an adenocystoma of the ovary. This was a firm, shapely circumscribed tumor which was identical with the tumor found in the wall of the uterus.

Peritoneum: There were the following pathological conditions of the peritoneum—tuberculosis in 4 cases, peritoneal cyst in 14 cases. In every case the cysts were due to adhesions about the tube and ovaries and were of the nature of retention cysts. One of these cysts contained cholesterin crystals and in its wall was a flattened tumor formation. On microscopic examination this was found to be made up of giant cells surrounding clear spaces in a stroma of new connective tissue. These giant cells had formed about the cholesterin crystals.

By vaginal puncture tissue was obtained in 7 cases which showed a pelvic hematocele in 2 cases and pelvic abscess in 5 cases, one of which was tuberculous.

Omentum: Sections from the omentum were normal in 3 cases. They showed a chronic omentis in 13 cases, and a share in a general tuberculous involvement of the peritoneum in 1 case. In another case there were two nodules of adenocarcinoma found in the omentum secondary to a fungoid tumor mass springing from the umbilicus which also showed adenocarcinoma.

GENERAL CONDITIONS.

In addition to these cases the following miscellaneous pathological conditions were met with:

Inguinal adenitis, suppurative, in	2	cases.
Inguinal adenitis, syphilitic, in	1	"
Tuberculosis of cervical glands in	3	"
Fibroma of skin of finger in	1	"
Adenofibroma of breast in	1	"
Cyst of the urachus in	1	"
Sac of femoral hernia in	1	"
Scar of a previous abdominal incision in	2	"
Hemorrhoidal tissue in	6	"
Ischiorectal abscess in	2	"
Fistula in ano, tuberculous, in	1	"

Tuberculosis in the female generative organs occurs in from 1 to 5 per cent. of the cases. In this series there were 18 cases (3%). The cervix, vagina and vulva, although occasionally affected were free from the disease in our cases. Th distribution of the tuberculous foci was as follows:

Uterus in	7	cases.
Ovary in	2	"
Tube in	11	"
Peritoneum in	4	"
Appendix in	1	"
Omentum in	1	"
Pelvic abscess (tuberculous) in .... (Origin not determined).	1	"

In one of these cases the tubes, ovaries, peritoneum and appendix were involved; in a second case the tubes, omentum and peritoneum; in a third case the tubes, peritoneum and uterus. In a fourth case the tubes and the ovaries were the seat of the disease; and in a fifth case the tubes and the uterus were tuberculous. In the remaining 13 cases but one structure was involved.

CONCLUSIONS.

1. Unsuspected cases which fully repay for the labor of routine work are discovered by systematised microscopic examination.

2. Although 20% of the cases showed a chronic endometritis yet in only 3.5% of the cases was the disease well marked.

3. Cervical polypi may give rise to very malignant tumors.

4. Psammoma bodies are not infrequently met with in inflammatory and papillary conditions of the tubes and ovaries.

5. In but few cases of tubal inflammations does the infection penetrate the tunica albuginea of the ovary.

6. Torsion of the pedicle was seen in three ovarian tumors.

7. Pathological conditions of the appendix were found in 63% of cases which were not operated upon primarily for disease of this structure.

8. Cholesterin crystals may give rise to giant celled formation about them.

9. The following unusual conditions were met with:
    (a) Squamous-celled carcinoma primary in a cervical polyp.
    (b) Sarcocarcinoma of a cervical polyp.
    (c) Ruptured papillary cystoma of the ovary with general carcinosis of the peritoneum.
    (d) Primary adenocarcinoma of the umbilicus with metastases in the omentum.

REPORT IN GYNECOLOGICAL PATHOLOGY.

BY DR. M. B. BONTA, LATE RESIDENT GYNECOLOGIST TO THE LAKESIDE HOSPITAL.

The following report is a résumé of the records in Gynaecologicol Pathology at the Lakeside Hospital from February, 1905, *to October,* 1906. *Certain cases of unusual interest are given in some detail.*

UTERINE LESIONS.

Curettings.—Uterine scrapings have been classified as follows:

Endometritis, acute	17 cases
Endometritis, chronic	92 cases

The acute form has been met with chiefly in cases of abortion.

Glandular hypertrophy	50 cases
Glandular hypertrophy with chronic endometritis	28 cases
Glandular hyperplasia	15 cases
Placential tissue (retained secundines)	30 cases

Carcinoma.—In 14 instances a positive diagnosis of malignancy was made from scrapings. Of these, 10 were instances of squamous-celled carcinoma and 2 of adeno-carcinoma; the 2 other cases—Nos. 1647 and 1656 probably belonged to the latter type.

Case No. 1764, in which the tissue was removed from the posterior vaginal wall was apparently a case of primary carcinoma of the vagina, as no involvement of the cervix was found at the time of operation.

In No. 1887, the findings were very suggestive of squamous-celled carcinoma; with this case and also No. 2010 (unmistakably cancer of the cervix) pyometra was associated—the only 2 instances in which this condition was met with.

Tuberculosis of the endometrium was found in 3 cases. In one of these (No. 1632) the process was far advanced as shown by the uterus itself; which was removed *in toto* at the time of the curettage. The other cases were in an early stage and gave typical pictures.

Curettings, in 56 instances, showed what we considered normal endometrium.

Under curettings may be mentioned:—

A case of unusual occurrence and interest—No. 1974—a hydatidiform mole. The specimen which was expelled from the uterus, consisted of a large amount of tissue that was characteristic of the growth in the gross and microscopically. There was no trace of a fœtus. The patient succumbed and a post-mortem examination was obtained. Sections of the uterus showed that the growth had in places penetrated the uterine vessels, and here and there had reinvaded the uterine musculature surrounding the venous channels in a way suggestive of malignancy.

A fuller report of the case will be made later.

Polypi.—Uterine polypi occurred in 9 instances, once in a uterus removed for carcinoma of the cervix.

Fibromyomata.—These were removed by myomectomy alone in 8 cases.

No. 1687 presented a submucous growth that had become infected. In the others the myomata were subperitoneal, and one of them (No. 1691) is worthy of special note. This was a supposedly simple fibroid tumor, measuring 4 x 5 cm., that sprang from the fundus by a rather narrow pedicle. On section the growth was found to have an outer layer or zone of fibromyomatous tissue surrounding a central and larger portion of the growth that showed a well-advanced adeno-carcinomatous structure. Uterine curettings, which had been obtained in this case prior to the abdominal operation, gave no evidence of malignancy. The patient is alive at the present time—more than a year after operation.

Fibro-myomatous uteri, removed by vaginal or supravaginal hysterectomy, furnished 23 specimens for examination. Most of these exhibited growths of both interstitial and subperitoneal forms.

The largest of the series was from case No. 1702. This was a multinodular tumor-mass weighing 3.5 kilograms; measuring 23 cm. from right to left, and 15 cm. anterio-posteriorly.

No unusual changes were met with in the uteri or tumors, hyaline degeneration in the latter was frequently noted, and the uterine wall in some cases showed chronic endometritic and metritic lesions.

Carcinoma.—Of 3 cases in which the uterus was removed on account of malignancy a squamous-celled carcinoma of the cervix was found in 2, and an adeno-carcinoma of the body in the third.

The *uteri* in 17 cases showed no other lesions than those incident to endometritis or senility. Hysterectomy had been done in the majority of these cases either on account of extensive adhesions in the pelvis or for the relief of prolapsus.

TUBAL LESIONS.

Acute salpingiits was found in 5 cases, all unilateral.

Chronic salpingitis, unilateral in 35, bilateral in 66.

Hydro-salpinx was seen in 14 unilateral and 12 bilateral cases. Both simple and follicular forms were noted.

Pyosalpinx was present in 14 unilateral and 31 bilateral cases.

There were 14 unilateral and 2 bilateral instances of tubo-ovarian abscess.

Perisalpingitis occurred in 31 unilateral and 114 bilateral cases.

Tuberculosis was present in 4 cases, all bilateral. No. 1632 is included in these. Here the mucosa of both tubes was almost entirely wanting; the outer walls were infiltrated with round cells; there were no giant cells. Reference has been made to the uterus of this case, in which the tuberculous process was demonstrable in the musculature. Tuberculosis of the endometrium was associated in 2 of the other 3 cases.

Tubal Pregnancy.—There were six instances of tubal pregnancy.

No. 1676 was a case of tubal abortion; the foetus was not found; chorionic villi and decidual tissue were present in the lumen of the tube This case was associated with intra-uterine pregnancy; abortion occurring on the day after the abdominal operation.

In a case of tubal rupture (No. 1817) both tubes showed a decidual reaction. A perfectly formed foetus of 3 months was found in the abdominal cavity connected with the placenta; the latter was partly attached to the posterior wall of the pelvis.

Rupture of the tube had occurred in No. 1842. Chorionic villi and decidual cells were present in hemorrhagic areas at the site of rupture. Intrauterine decidual reaction was also demonstrated. Both tubes were removed and showed a chronic salpingitis.

No. 1881 was a large pelvic hematocele that was treated per vaginam. Chorionic villi undergoing degeneration were present in the tissue.

In No. 2002 the outer walls of the tube were infiltrated with blood, throughout which chorionic villi and decidual cells were scattered; the main lumen of the tube contained no trace of the pregnancy. The opposite tube showed the presence of accessory lumina. These findings give additional evidence in support of the observation that accessory lumina may be an etiological factor in tubal pregnancy.

Pregnancy had taken place in the main lumen of the tube in No. 2007. The tube walls were intact. Chorionic villi were well preserved.

Normal tubes were found in 22 cases, the greater number of these being removed in hysterectomies for fibroid and other conditions.

OVARIAN LESIONS.

Of these the most frequent was perioophoritis, which occurred in 63 unilateral cases. There were 20 unilateral and 3 bilateral cases in which oophoritis was the diagnosis, the inflammatory process here extending into the substance of the ovary.

So-called "cystic degeneration" or preferably "follicular hypertrophy" was observed in 36 unilateral and 10 bilateral instances.

In 26 cases normal ovaries were found—in only 3 bilateral—nearly all being removed with other pelvic structures for various lesions. Calcification had taken place in 2 cases, in both associated with uterine fibroids.

Cystomata. There were 14 specimens, classified as follows:

Multilocular cysts	3
Unilocular cyst	1

These four were of rather unusual size, the largest containing twenty-six litres of fluid. 2 were of the papillomatous variety. All were lined with columnar epithelium.

Intraligamentary cyst	1
Graafian follicle cysts	5
Dermoid cysts	4

The dermoids varied in size from 6-11 cm. in diameter; all had characteristic contents, chiefly hair and sebaceous material, some showing cartilage, sweat glands, etc. in their walls. In one of them (No. 1952) torsion of the pedicle had taken place, leading to a hemorrhagic infiltration of all the lateral structures on this side of the pelvis.

No. 1810 was probably a case of a adeno-carcinoma of the ovary. There was a large quantity of ascitic fluid present; the pelvic structures were matted together by a papillary growth and metastases were found in the omentum and parietal peritoneum. Tissue removed for diagnosis showed an adeno-carcinomatous character.

A very rare case, which will be more fully considered in another report, was one of ovarian pregnancy No. 1778.

Partly imbedded in the ovarian stroma was a blood-clot the size of a walnut. Sections of the clot showed chorionic villi. The ovary itself contained a very recent corpus luteum. There was nothing in the tube on this side to indicate that the pregnancy had originated in it. The opposite tube and ovary were normal-appearing.

LESIONS OF THE APPENDIX, AND MISCELLANEOUS CASES.

There were 2 cases of suppurative appendicitis with perforation.

A diagnosis of chronic appendicitis was made in 71 cases. Many of these would be regarded by some as normal.

Periappendicitis was present in 32 cases.

Obliteration of the lumen was found in 25 instances.

65 specimens were considered normal.

Of miscellaneous cases there were:

Adeno-carcinoma of the breast	1
Tuberculous glands of the neck	1
Gall-stones	1
Cyst of Bartholin's gland	1
Urethral caruncle	1
Suppurative inguinal adenitis	1

REPORT IN GYNECOLOGICAL PATHOLOGY.

BY ALBERT J. BOWER, M. D.

Late Resident Gynecologist to the Lakeside Hospital.

A *résumé* of the records in Gynecological Pathology at the Lakeside Hospital from October 1906 to October 1907, certain of the more interesting cases being given in detail.

UTERINE LESIONS.

CURRETTINGS.—Changes in the endometrium have been classified as follows:

Glandular hypertrophy	22
Glandular hyperplasia	7
Acute endometritis	7
Sub-acute endometritis	9
Chronic endometritis	47
Glandular hypertrophy with hyperplasia	4
Glandular hypertrophy with chronic endometritis	17
Glandular hypertrophy with sub-acute endometritis	1
Glandular hypertrophy with hyperplasia and chronic endometritis	8
Glanduler hyperplasia with chronic endometritis	2
Chronic endometritis, with added acute changes	3
Normal endometrium—including oedema and menstrual changes	25

Decidual and placental tissues were present in 29 cases, all but two of which showed a cellular infiltration of varying degrees. The diagnosis of decidual endometritis—the endometrium being fairly well preserved, but decidual cells present throughout the stroma—was made in 7 cases. There were 2 cases of pyomerta, in which the endometrium contained a purulent exudate in addition to other evidences of a chronic inflammatory process, but no malignancy could be detected.

Carcinoma cervicis of the epitheliomatous type were recognized in 5 instances.

Adenocarcinoma of the body of the uterus was found in three cases. In one of these a polyp was removed which also showed the malignant process found in the endometrium. Gyn. Path. No. 2227 showed a malignant condition of the glands of the endometrium. There were, in addition, several pieces of tissue whose relation to the endometrium was not clear, this tissue showing numerous cell nests composed of rapidly proliferating high columnar and fusiform cells arranged about the walls of blood-vessels, suggesting a perithelioma. However, no direct outgrowing of the cells from the blood-vessel walls could be traced, so that a positive diagnosis of the latter condition could not be made. (As the patient lives some distance from the city a second curretting for further diagnosis could not be done).

Fibromyomata uteri occurred in 16 cases. Myomectomy was done in 6 cases, in 2 of which submucous growths were removed per vaginam, 4 subperitoneal tumors being removed by laparatomy. None of these were large. Hysterectomy, vaginal, supravaginal, or combined, was done in the remaining 10 cases. One of the uteri contained all 3 types of tumors—submucous, interstitial, and subperitoneal—while several of the others contained 2 varieties. In one a sloughing submucous growth had been curetted for diagnosis—the condition having been suggestive of malignancy—and a vaginal hysterectomy was done later for a general myomatous condition. None of the tumors showed any malignant changes; several showed an inflammatory condition, generally a superficial change in a submucous tumor. Hyaline degenerations were common, and calcification was present in one case.

In Pathological No. 2188 we curetted 17 days before hysterectomy was performed, and diagnosed a chronic interstitial endometritis with giant cell formation; later sections from various areas of the myoma showed no changes other than those of a superficial inflammatory process.

Pathological No. 2283 was a particularly interesting case. There was a large submucous myoma with a superficial inflammatory condition, and a hematosalpinx of the right tube—due to a tubal pregnancy—in which degenerated chorionic villi and a few placental buds or giant cells were seen.

Carcinoma: There were 2 specimens of squamous-celled carcinoma of the cervix removed by vaginal hysterectomy. These cases presented similar conditions and were very interesting; they will be discussed more fully in a later report. Path. No. 2113 showed a cauliflower growth 4.5 x 4 x 2.5 cm. springing from the posterior cervical lip, growing downward into the vagina but not upward into the body of the uterus, and laterally only to a slight extent. The uterus was but slightly enlarged and there was no induration in the broad ligaments or extension to the vaginal wall. Histologically the growth showed a typical squamous-celled carcinoma of the cervix, confined entirely to the lower portion of the posterior cervical lip, not extending upward to the level of the internal os, and with no involvement of the anterior lip. Sections from various portions of the uterus showed a mild grade of metritis and endometritis, with a slight glandular hypertrophy.

Path. No. 2134 showed the same condition, except that there was a very early malignant change in the anterior lip. The upper portion of the posterior cervical lip was not involved, however, and the body of the uterus showed a normal muscle wall with glandular hypertrophy and chronic endometritis.

Hysterectomy, for other conditions than carcinoma or myoma, was done 9 times in cases of marked descensus or adhesions. The histological findings were those belonging to endometritis or perimetritis.

Metritis was found in 14 cases. In addition to those just mentioned, this condition was found in myomatous uteri—and once in a carcinomatous uterus—in areas not involved in the tumor growths.

Among other conditions of the uterus were: 3 fibrous polypi in the uterine cavity, 1 showing myxomatous degeneration; 3 cervical polypi; there were 2 cases of diffuse fibrous tissue increase in the muscle wall; 1 of a diffuse muscular hypertrophy; 8 cases showing cervical endometritis or endocervicitis; also Nabothian follicles, hypertrophy of the cervix and glandular hypertrophy.

TUBAL LESIONS.

Chronic salpingitis occurred in 16 unilateral and 25 bilateral instances.

Subacute salpingitis in 8 unilateral and 3 bilateral cases.

Hydrosalpinx—7 unilateral and 2 bilateral.

Pyosalpinx—12 unilateral and 24 bilateral.

Several cases seemed to show an intermediate stage between pyosalpinx and hydrosalpinx, there being a thin exudate in the main lumen of the tube, while in the crypts between the folds of mucosa could still be seen a small amount of purulent exudate, which had not been entirely resolved. Path. No. 2276 shows a tube with a typical pyosalpinx in a section taken from the ampulla, while the fimbriated extremity, in a mass of adhesions on the surface of the ovary, shows a typical hydrosalpinx.

Tuberculosis of the tube was present in 2 instances, 1 unilateral, and 1 bilateral. Path. No. 2056 showed a chronic salpingitis, bilateral; in the mucosa and under the peritoneal coat there were numerous miliary tubercles, giant cells and some caseation. Dense adhesions united the right tube and the ovary, and in the adhesions and extending into the hilus of the ovary were seen tubercles and giant cells. The tuberculous process, however, had not extended into the ovarian stroma. Path. No. 2066 was a bilateral pyosalpinx showing a few small tubercles in the mucosa and subperitoneal tissue of one tube, without giant-cell formation or caseation; the other tube showed no tuberculous process.

Perisalpingitis was present in 23 unilateral and 56 bilateral instances.

Tubo-ovarian abscess was diagnosed in 2 unilateral and 1 bilateral case. Several others, which clinically were classified as tubo-ovarian abscess, have been included separately under pyosalpinx and ovarian abscess.

Tubal pregnancy: 4 cases were clearly demonstrated while two others, treated per vaginam, were undoubted instances of the same condition.

Path. No. 2038 showed a hematosalpinx, with chorionic villi in the clot, the epithelium of the villi being regularly arranged in a double layer. Both tubes showed a chronic salpingitis; the patient was operated upon for a chronic inflammatory condition, there having been no history suggestive of an ectopic pregnancy.

Nos. 2052 and 2114 were treated by vaginal puncture; blood clots removed from the cul-de-sac, showing degenerated decidual and placental tissues.

No. 2148 showed a hematosalpinx; decidual cells were present in the wall of the tube, but no villi were seen. The other tube was normal. Placental tissue was present in a blood clot free in the cul-de-sac, and decidual tissue in the uterine scrapings.

In No. 2204 there was a hematosalpinx showing chorionic villi in the blood clot. No decidual cells were seen in the wall of the tube. Both tubes showed a chronic salpingitis.

No. 2283 was noted under myomata of the uterus.

Normal tubes: 15 were removed during the year, in connection with hysterectomy or ovarian cystectomy.

OVARIAN LESIONS.

Perioophoritis was present in 44 unilateral and 19 bilateral instances, the inflammatory process here being sharply limited by the tunica albuginea; this was the most frequent pathological condition of the ovary.

Oophoritis was present in 18 unilateral and 8 bilateral instance.

Ovarian abscess—7 unilateral and 1 bilateral instance.

Follicular hypertrophy occurred in 42 unilateral and 11 bilateral cases. The entire ovary was rarely removed for this condition alone, the cystic portion alone being resected.

Corpora lutea were noted in 14 cases; atrophy or sclerosis in 5: senile ovary in 6; normal ovary in 2.

No. 2149 was an adenocarcinoma of the ovary, in a patient aged 23, of at least 1½ years' standing. This case will be reported more fully later.

Cysts: 13 cysts were removed during the year from 11 patients; in two of these the condition was bilateral.

Graafian follicle cysts	5
Cospus luteum cysts	4

Adeno-cystoma 2, lined by a distinct single layer of columnar epithelium.

Dermoid 1, containing sebaceous material, hair, teeth and cartilage.

No. 2167 was an interesting case. Projecting from the lower pole of the ovary was a sac which measured—collapsed—10 x 5 cm.; it contained a thin, purulent material. Microscopically, the wall of the abscess was densely infiltrated with pus cells so that the lining epithelium could not be made out distinctly, but it appeared to be an infected cyst—possibly, from the gross appearance, a parovarian cyst.

APPENDIX LESIONS.

There were 3 cases of acute appendicitis, 2 of which were suppurative; 2 of subacute, and 37 of chronic appendicitis. Periappendicitis was present—sometimes very slight—in nearly every case.

There were 12 cases of occlusion of the lumen—with and without inflammatory changes; 1 of polyp of the mucosa; 2 with concretions. 33 specimens were considered normal. Tuberculosis of the appendix was found in 1 case. No. 2244 showed a purulent exudate in the lumen and a marked cellular infiltration throughout the entire wall, with an increase in the fibrous tissue. In the submucosa and muscularis small tubercles and many giant cells were seen. The section suggests an acute change added to a chronic inflammatory process. Neither the right nor the endometrium showed any tuberculous process.

MISCELLANEOUS CASES.

Condylomata of the vagina (small); 2 cases. One showed a chronic inflammatory process, not characteristic. No. 2074 showed a chronic inflammatory condition, with several giant cells and areas of epithelioid cells, but no definite tubercles and no caseation; it was impossible to classify the specimen positively as tuberculous or syphilitic. There was nothing in the history or physical examination of the patient to aid in the diagnosis.

One specimen showed metastases to the vaginal wall of a carcinoma of the cervix.

Urethral caruncle, 1.

Labium minus cyst, 1. No. 2112 was a unilocular cyst, 5.5 x 5 x 4.5 cm., attached by a short, broad pedicle to the left labium minus; it contained a thick dark fluid which was probably sebaceous material into which hemorrhage had taken place. The cyst cavity was lined by a single—though indistinct—layer of columnar epithelium.

Nephritis, 1. In No. 2285, the kidney, 13 x 10 x 7 cm., contained 2 large, irregularly shaped black calculi and several abscess cavities. Sections showed a chronic parenchymatous and interstitial nephritis, with an acute process superadded; pyonephrosis was also present.

Specimen of intestinal wall, 1, showing an inflammatory process with hemorrhage into the wall and necrosis.

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ETIOLOGY OF ECTOPIC GESTATION[1]

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ALTHOUGH in the past several years there has been accumulating a considerable amount of literature on the subject of ectopic pregnancy, the major part of it has dealt chiefly with the clinical and the operative phases of this anomalous condition, whereas the histopathological features, though of great importance, have been relegated to the background or have been entirely neglected. Thus it has come about that the therapeutic and operative treatment of ectopic pregnancy is pretty generally understood, and as this part of the subject does not fall within the scope of this paper, I shall do no more than allude to it.

There is a wide divergence of opinion amongst competent observers in regard to the abnormal changes in the Fallopian tube that are held responsible for the causation of tubal pregnancy. Some investigators attribute its occurrence to the existence of congenital[2] anatomical perversions in the structural formation of the tube, such as accessory ostia, persistence of the convoluted fœtal type of Fallopian tube, constrictions, flexions and other abnormalities. Others attribute it to lesions or changes that have resulted from an inflammatory process involving the pelvic organs, and more particularly the Fallopian tubes.

It is extremely difficult to arrive at the true cause of this not infrequent anomaly and at the best our ideas must be, to some degree, mere conjecture for the reason that, with a few exceptions, it is almost impossible to demonstrate just what lesion, congenital abnormal conformation, or pathological abnormality is presented by the tube at the exact site occupied by the ovum. The main difficulty lies in the fact that the pathologist is rarely able to make his observations until the condition has progressed so far that the original anatomical features have been obliterated or so altered that the recognition of the factor predisposing to the starting or development of the tubal pregnancy is obscured or rendered impossible.

Nevertheless, despite the existence of seemingly insuperable difficulties it is our duty to continue our researches in this almost unknown field, for not until we clearly understand the predisposing factor, or factors, which bring about an ectopic gestation, can we hope to institute a more intelligent preventive treatment that will result in a lessened morbidity or at least a lessened mortality.

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[1] Read before the Clinical and Pathological Section of the Cleveland Academy of Medicine, March 6, 1908.

[2] Since the completion of this paper, it has been my good fortune to operate upon a case of ectopic pregnancy, in which the very conditions that I have referred to principally from the histological point of view, were found (Figs. A, B, and C). See p. 4.

From the history of the case and of the attack incident to the extrusion of the ovum through the os fimbriæ (tubal abortion) a pre-operative diagnosis of ectopic pregnancy was made. The opposite tube was removed as a prophylactic measure; the pathological changes in it will be described in a subsequent paper. The patient made a good recovery.

The different observers, though they disagree in their views in regard to the remote causative factors of an ectopic pregnancy, are almost a unit in believing it to be due to some mechanical interference in the descent of the ovum through the tube lumen.

Only by pathological studies of these cases can we hope to arrive at a correct etiology but, as has been said before, the pathological reports are meagre or lacking so far as the histological features are concerned — the clinical and operative side being dealt with more fully. The clinical phases of the question, of course, are important and must be studied in conjunction with the histological changes. Clinical observation tends to confirm the view that an inflammation involving the pelvic structures has generally preceded the occurrence of an ectopic tubal pregnancy, though on this point, as one would expect, all are not agreed.

Reed says, to quote his own words, "The question arises, what cause or causes are responsible for an impregnated ovum remaining and becoming implanted in the tube, instead of passing into the uterus? Certain alleged causes formerly frequently cited as responsible for tubal pregnancy, such as inflammatory diseases of the uterus and tubes, must be absolutely discarded. We know that these conditions, instead of being the cause of tubal pregnancy, make a woman sterile for the time being and therefore exclude tubal as well as normal uterine pregnancy." I think you will agree with me that this conclusion is inaccurate and, as I shall demonstrate later, a tubal pregnancy is practically always preceded by an inflammatory reaction and in many cases by a period of sterility which, however, is only relative as the occurrence in nearly all of these cases of a delayed pregnancy would denote. Martin, who formerly held to the view that an inflammatory condition was responsible for the occurrence of an ectopic gestation now considers that it results from some mechanical interference with the descent of the ovum not necessarily, if ever, produced by an inflammation. On the other hand Dührssen considers tubal disease, particularly that due to a gonorrhœal infection, as the most frequent cause of extrauterine gestation. Schauta has advanced the theory that catarrhal, and especially gonorrhœal processes involving the tubal mucosa, predispose to the condition; and Küstner is of the same opinion.

When one studies these cases from a combined clinical and histological standpoint it is difficult to arrive at any other conclusion than that an inflammatory affection is responsible for the onset of an ectopic pregnancy and in fact the weight of opinion based on careful observation and study supports this view.

One might be inclined to believe that cases of ectopic pregnancy were more frequent now than formerly, but this is not true. The apparent increase in the number of cases is due to better and surer methods of differential diagnosis and to the success of operative procedures carried out for the relief, cure, and sometimes for the diagnosis of the condition. Operations disclose many cases hitherto unsuspected.

The human organism alone, from data obtainable, suffers from ectopic gestation with all its sequences and complications. The lower animals are seldom, if ever, similarly afflicted. Bland Sutton[1] says: "I have made a careful study of the records and available specimens of extrauterine gestation in what are called the lower animals and quickly satisfied myself that tubal pregnancy in them is very rare; indeed, I have failed to find a single convincing record or specimen, but there are very many cases recorded in which puppies and kittens inclosed in tightly fitting sacs have been found adherent to the omentum and intestines."

His explanation is, that in mammals with two-horned uteri the horns are of the same length and often contain several fœtuses. When the fœtuses are too large to traverse the maternal passages, the uterus, as a consequence of its violent efforts to expel its contents, ruptures and the fœtus or fœtuses are extruded into the abdominal cavity. He found that although in many instances the animals die, in some cases they survive.

Reasoning from the results of his investigation of the subject we see that there must be distinct pathological changes in the human Fallopian tubes, that are seldom produced or found in those of the lower animals, to account for the occurrence and frequency of the condition in women. That an inflammatory condition alone might be capable of producing this wide variation between the lower animals and the human being is a proposition certainly worthy of consideration. We may ask why it is that the lower animals are so seldom if ever afflicted by this trouble. The only plausible explanation or answer must be that inflammatory affections of the adnexa are frequent in the women, while in the lower animals they are just as infrequent. Gonorrhœa is probably the chief predisposing cause, nevertheless all inflammatory affections, including those of tuberculous nature, play their part in producing conditions which favor an

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[1] London Lancet, Dec., 1904.

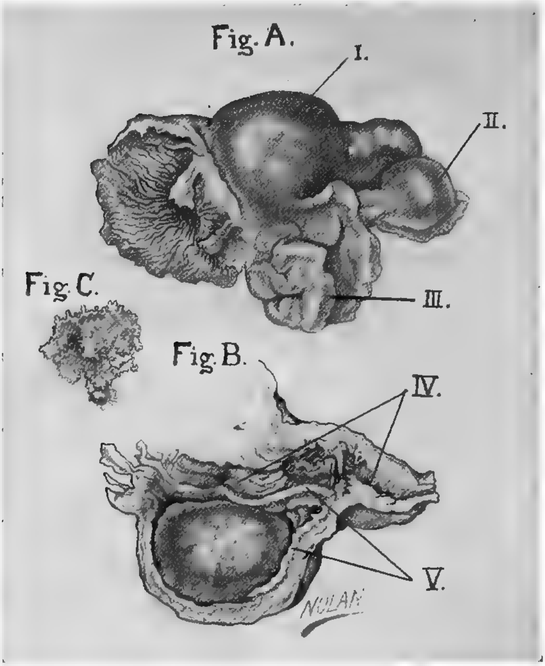

Fig. A shows a very large flared fimbriated tubal extremity with the longitudinal arrangement of the folds of the mucosa well marked. The hypertrophied tuft or tag of folds protruding at one point from the os fimbriæ represents the continuation of the folds (Fig. B, No. 5, upper line), that comprises the wall of the false diverticulum within. In the drawing in shape it suggests an accessory tube. The remaining border of the fimbriated end has somewhat ragged, thin edges, indicating in my opinion, the places at which they were adherent previous to the expulsion of the ovum, the tube being occluded except at the entrance to the false canal or diverticulum. It is often noted that a previously occluded tube opens first at an angle from which the mucosa appears to pout outward.

No. 1 shows a protuberance or a bulging of the wall of the tube on its anterior phase. This indicates the former site of the ovum enclosed in the hæmatoma.

No. 2 represents the cornual extremity of the tube with a nodular enlargement, a so-called "salpingitis nodosa." The condition is simply an irregular thickening of the wall due to the inflammatory infiltration and hyperplasia at this point.

No. 3 shows a fair-sized ovary with an irregular surface. It is intimately adherent to the mesosalpinx (which is infiltrated, thickened, and almost obscure) and to the tube. Except for adhesions the ovary macroscopically appears normal.

Fig. B shows the interior of the tube (No. 1) incised along its superior border — opposite its mesenteric attachment.

The irregular thickness of the tubal wall is noticeable, as well as the general increase in the size of the interior of the tube.

No. 4 indicates the course of the main central lumen of the tube which narrows as it approaches the cornual end but is patent throughout.

In the portion of the mucosa between the two lines (4) adhesions are seen extending from one side of the lumen to the other and between the individual irregular folds.

No. 5 shows very plainly the inner wall of an adjacent, parallel canal or obstruction, and the consequent retention and development of the ovum within the Fallopian tube. An ectopic gestation in the ovary may be due purely to some simple obstruction to the extrusion of the ovum from the Graafian follicle wholly independent of any inflammatory process.

I had the good fortune some time ago to operate upon a case[1] of true ovarian pregnancy in which not only the ovaries but also the Fallopian tubes were macroscopically free from any inflammatory reaction. Histologically neither the tube nor the ovary removed showed any evidence of the existence of any inflammatory process. The right ovarian tumor with the Fallopian tube I removed, and saved the left tube and ovary. One year and eight months afterward the patient gave birth to a full-term child, having had a normal labor.

In this case, therefore, the ovarian pregnancy seems to have been due to the non-liberation of the ovum from its Graafian follicle, the spermatozoon having gained an entrance, and fertilization and development then having ensued, while the ovum remained *in situ*.

I need hardly refer to the anatomical structure of a normal Fallopian tube. The peritoneal coat lies externally, the mucous layer internally, while between the two are the two strata of muscle tissue, the longitudinally arranged layer without and the circularly placed layer within. This muscle tissue endows the tube with a peristaltic power which is available in the propulsion of the ovum along the mucous-lined canal. In the majority of inflammations of the tubes (which are practically always bilateral) marked changes ensue. The infection travels from within or from the mucosa outward through the muscular coats to the peritoneal surface, although before this has occurred infectious material may escape from the fimbriated extremity of the tube and involve the surrounding peritoneal surfaces of the adjacent or remote pelvic and abdominal

[1] To be reported later.

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diverticulum (false) to which I have referred throughout my paper. The funnel-shaped diverticulum is patent at the distal or fimbriated end but is occluded at its mesial extremity.

The cut edges of the hypertrophied mucosa forming the inner wall of the diverticulum are distinctly seen.

The upper line in No. 5 shows a continuation of the incised mucous fold (forming the wall of the diverticulum) with an intact hypertrophied fold which runs longitudinally to the extreme limit of the fimbriated extremity of the tube.

The hæmatoma, which measured 3.8 x 2.5 x 1.9 cm. in size, is shown in the figure occupying the dilated or pouched diverticulum (No. 5), from which however it has been previously extruded. On section this mass presented the developing ovum, at an early stage, imbedded in it. The site of the ovum in this case determined whether a rupture of the tubal wall or a tubal abortion was likely to occur. The latter came about.

Fig. C represents a piece of chorionic membrane with its chorionic villi well developed. It was found incorporated in a piece of blood clot removed at the time of the operation.

viscera. We find the surface epithelium of the mucosa of the tube swollen, infiltrated, and in part degenerated and desquamated; here and there the cilia have been destroyed. Very often in the acute and subacute processes a purulent exudate partially or completely fills and distends the lumen of the tube. This purulent exudate not only serves to harbor some of the invading bacterial organisms where they may later be annihilated by the leucocytes and by their own toxins, but would appear to serve another equally important purpose by keeping the mucous surfaces separated and preventing their coalescence which might result in a partial or complete destruction or obliteration of the tubal canal. In other words it apparently serves to maintain the patency of the lumen of the tube.

This fluid exudate may also serve another purpose. After the subsidence of the inflammation, and the destruction, disintegration, digestion, and absorption of its cellular elements, a so-called hydrosalpinx often results so that the lumen of the tube remains filled with a clear, pale, or generally yellowish fluid. As the fimbriated end by its freedom of movement, its increased size, and specific gravity, gravitates downward in the pelvis toward the cul-de-sac of Douglas, unless prevented by adhesions or otherwise, the fluid contents will tend to exert a constant pressure toward the occluded fimbriated extremity of the tube. This fluid pressure from within serves, I believe, to render the tube again patulous at the abdominal ostium, the patency being brought about more quickly in this than in any other way. The reopening of the distal end of the canal makes it possible for the tube to functionate again in transmitting the ovum. I have met with cases in which a small hydrosalpinx was present on one side and the opposite tube showed either a small opening at one angle of the almost totally occluded extremity or an almost completely restored ostium. At the narrow orifice the mucosa is usually found pouting and a histological examination of such a specimen would reveal the existence of a tube in which the fimbriated extremity had been occluded. The stroma of the mucosa together with the muscularis and the peritoneal coats of the tube shows varying degrees of infiltration and reaction according to the degree and the character of the inflammation present, although in most instances a certain amount of fibrous connective tissue is produced, as a result of the inflammatory reaction in the wall of the tube. Seldom does this tissue entirely supplant the entire muscularis even though much of the latter has been destroyed. Inasmuch as some of the muscularis can nearly always be demonstrated histologically, it is conceivable that peristaltic motion might still be possible although more or less impaired by the diminution in the number of muscle bundles and the increased amount of connective tissue. The mere adhesion of a tube to the surrounding tissue to some extent might interfere with peristaltic action, but could not wholly prevent it. Hence it is possible to have peristalsis of the tube after most inflammatory affections except when the tube is distended by a fluid or a semifluid exudate which temporarily impairs its functions, and puts it at rest so far as peristaltic action is concerned. We find in a salpingitis that almost always folds of the mucosa become adherent to those adjacent and at times to those projecting from the opposite side of the lumen. However, it is more usual to see them adhere in a parallel direction with the neighboring folds. When the lumen of the tube is distended by a fluid exudate, as is commonly the case, some of the smaller folds are partially or wholly obliterated by the resulting stretching of the wall. This also appears to be a conservative process to prevent coalescence of more mucous folds and thus an effort to further preserve the patency of the main lumen.

As the longitudinal folds of the mucosa in a salpingitis coalesce together in a parallel direction the epithelium enclosed by their cohesion is generally found in a well-preserved condition or, if it has been partially destroyed, it has been entirely regenerated owing to the protection afforded. The cilia are usually present — at least in part. By the cohesion of portions of the longitudinal folds of the mucosa and the consequent preservation of the enclosed epithelium which comprises the surface of the folds, epithelial-lined loculi and gland-like channels or canaliculi are formed. The former consist of spaces which may become distended with fluid to form cystic loculi. The latter or the canaliculi may be patent at one or both extremities, but more often are blind at the mesial and open at the distal end. The fluid exudate in the tubal canal proper serves to keep open the end of the canal nearest the fimbriated extremity. These canals may be superficially placed in relation to the lumen of the tube, or they may occupy a position deep down beneath the surface epithelium or near the peritoneal layer. In the latter case there has been a hyperplasia of the connective tissue where the edges of the folds have adhered and thus the epithelial channels or loculi have been forced outward until they appear to occupy a position in the center of the thickness of the tubal wall or even farther outward. In a number of instances they are completely surrounded by a zone of connective tissue of varying thickness whose component cells are of more or less recent formation. The tendency is for the folds to adhere and give rise to the formation of these canals on the side of the tube opposite to the one towards which the fluid exudate gravitates when the exudate is insufficient in amount to distend the tube. In a similar manner the patency of the distal end of the canal — as opposed to the mesial or upper end — is maintained by the fluid which gravitates and exerts pressure toward the lower dependent or cœlomic end of the tube — preventing the tubal walls from coming together. These canal formations must not be classed with accessory tubal lumina, true instances of which are rarely met with. Most of those described in reality are not genuine but appear in sections of a much convoluted, persistent fœtal type of tube, the wall of the tube with its lumen having been incised twice in the same transverse or oblique plane so that there is brought into view what has been erroneously thought to be a second or branching lumen.

One occasionally finds the epithelial or duct-like remains of the Wolffian body coursing superficially along the wall of the tube, but these are generally situated nearer the external surface and are readily distinguished by the character of their structure.

To these epithelial-lined canals which are formed by the coalescence and cohesion of the folds of the tubal mucosa and by the inclusion of their epithelium I have given the name of false diverticula as opposed to the true diverticula of which I have had the opportunity of seeing only a few in the macroscopical and microscopical examination of many thousands of normal and pathological specimens. The presence of true diverticula seems to be one of the rarest of tubal malformations, whereas false diverticula are found in a large percentage of tubes as a result of inflammatory affections. There is no other structural (pathological or congenital) change in the Fallopian tubes so constantly present which could account for the occurrence of the anomaly known as ectopic or tubal pregnancy except possibly the partial absence of cilia or the infiltration and alteration of the tubal wall, by which peristalsis is impeded. But both are of themselves insufficient factors. My attention was first drawn to the formation of these false diverticula about six years ago, since which time much study and observation have only served to strengthen the conviction that in the greater percentage of cases of tubal ectopic pregnancy the explanation is to be found in this coexistence.

Recently Opitz[1] has drawn attention to the formation of these false channels or culs-de-sac formed by the adhesion of neighboring folds of the mucosa brought about by inflammatory affections within the tube. On making serial sections of the tubes in 23 cases of ectopic pregnancy he found that these canals or false passages were present in every instance. He looked upon them as lodging places for the ovum and held that their existence afforded a possible explanation for the occurrence of ectopic pregnancy. Landau and J. Whitridge Williams have referred to what may be called true diverticula found occasionally in the wall of the tube. The latter says "In connection with the normal anatomy of the tube I desire to call attention to an abnormality in its development which may bear a causal relation to the production of extrauterine pregnancy. I refer to diverticula extending from the lumen into the wall of the tube reaching almost to its peritoneal covering. They are lined by the typical single layer of ciliated epithelium and correspond in all respects to the structure of the normal lumen of the tube. They should not be confounded with the so-called accessory ostia of the tube; for, unlike them, they do not open on the outer surface of the tube and, on simple inspection, give no evidence of their existence. I have observed this anomaly on two occasions."

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[1] Zeit. für Geb. u Gyn. 1903. Bd. xlviii.

He further states in reference to these diverticula "How often similar formations occur I am unable to state, for I have only found them twice and the only reference to them in the literature was made last year by Landau and Rheinstein who found a similar case."

Williams is inclined to think that a number of his cases of tubal pregnancy had so developed, but upon further examination he believed a more satisfactory explanation was that the fertilized ovum had burrowed beneath the mucosa "just as it does into the decidua in uterine pregnancy."

These structures branching off from the main lumen, I have noted in a number of cases. In two or three instances they were true diverticula but the greater number of them could be explained by a cross-sectioning of a convoluted fœtal type of tube twice in the same plane. The mucosa in the former is arranged in the form of folds similar to those seen in the main lumen of the tube. The mucosa of the false diverticula, however, is not arranged in the form of folds, the epithelial layer being very evenly and closely attached about the periphery.

Henrotin and Herzog have reported a case of ectopic pregnancy occurring in an accessory tube which had its origin from the side of the main Fallopian tube with the canal of which its lumen did not communicate. This case undoubtedly was due to the obstruction to the entrance of the ovum into the main lumen through the accessory ostium.

Webster holds that a "decidual reaction" occurring in an abnormal tube is responsible for the retention and growth of the fertilized ovum within it. This theory is plausible and on first thought might seem to carry some weight as an etiological explanation, but on closer analysis is untenable. I am inclined to believe that the ovum in a normal pregnancy when it reaches the interior of the uterine cornu, where the continuity of the tubal canal with the uterine cavity forms an inverted funnel, is blocked in its further descent into the uterine cavity by the hypertrophic changes which ensue in the corporeal endometrium preparatory to the reception of the fertilized ovum. The ovum then plays the part of a parasite, in its efforts to obtain nourishment and to live, by attaching itself to the mucosa which is later converted into a decidual membrane into which penetrate the chorionic villi. The growth of the ovum at this point very often causes a protuberance or a so-called gibbous condition of the uterine cornu which is often of value in the diagnosis of pregnancy. The author has had a number of cases of normal pregnancy in which this inequality of the two cornua could be readily made out on palpation at the 2nd to the 3rd month; the ovum afterward grows downward in the direction of least resistance.

The reaction occurring within the tube is very slight as compared with that in the uterine mucosa and by itself would be quite incapable of completely blocking the ovum in its passage toward the uterine cavity. In tuberculous Fallopian tubes, in which ova have lodged and developed to form an extrauterine pregnancy, one would look for a very slight "decidual reaction" as a consequence of the limited vascularity and the destruction wrought by the tuberculous process. In most of our cases of tubal pregnancy the formation of a decidua, resembling the decidua vera of the uterine cavity, could be demonstrated but only at the site of the ovum and then over a very limited area.

In regard to Webster's explanation Kelly says: "Against Webster's theory, which Patellani and Moericke have endeavored to support, lies the insuperable objection that we know of no animal in which the uterine tube functions as a uterus." Bland-Sutton in the study of a number of specimens in the lower animals, in addition to the records in a number of cases, was unable to find one authentic case of extrauterine pregnancy. Schauta, Dührssen and others believe that inflammatory processes within the tube predispose to the development of an ectopic gestation.

Opitz has been able to demonstrate in a series of twenty-three cases the presence of diverticula from the main lumen, resulting from the union of the longitudinal folds of the tubal mucosa due to inflammatory affections. We have found these false diverticula or channels not only in every tube in which the ovum had rested but also in the tube on the opposite side. The inflammatory reaction in every case had been bilateral. Some of the tubes showed evidences of a previous inflammation which had entirely healed, the anatomical changes alone remaining to indicate its pre-existence (cases of so-called "healed" salpingitis). Cases of ectopic gestation have been reported coexisting with a fibroma of the isthmus tubæ and again when polypi have been found in the lumen of the tube or at the cœlomic ostium. External migration of the ovum which occurs not infrequently — the ovum passing from one side of the pelvis and entering the tube of the opposite side — has been advanced as one of the causative factors. It is believed that the ovum during the time consumed in its intrapelvic transit has gradually become so large that its propulsion along the entire length of the lumen of the Fallopian tube is impossible, and its progress is therefore arrested. External migration of the ovum has been observed many times, the corpus luteum being found in the ovary of the side opposite to that on which the ectopic was found. In fact Küstner noted the occurrence of external migration of the ovum seven times in a series of twenty-five cases, showing that it is not at all infrequent.

Where the ovary of one side and the tube of the opposite side have been extirpated not only true but ectopic pregnancy may result, external migration of the ovum being necessary.

While external migration serves to draw our attention to an absence of the tube or a pathological condition of the tube opposite to that in which the ovum finally rested, it proves only that a relatively greater impairment existed in the tube or that the tube was entirely absent on the side on which the ovum was liberated, or that the os fimbriæ of the tube on the opposite side was more accessible. Peters and others have proved that no chorionic villi are developed until the ovum has been nourished for a certain time by the decidua formed in the tube. In most instances the corpus luteum is found in the ovary on the same side as the tube lodging the ovum.

Hensen has shown conclusively that conception in women takes place in a manner similar to that in animals, the ovum in each case being fertilized in the ampullary portion of the tube, every pregnancy thus being primarily and temporarily at least an extrauterine pregnancy. He has also demonstrated that in dogs, rabbits, and guinea pigs the ovum remains several days in the Fallopian tube.

With the ovum normally retained for a number of days within the tube and with possibly an intrapelvic external migration, an impairment of peristaltic propulsion, a partial destruction or absence of the cilia, an ectopic pregnancy might result.

The corroding action of the ovum when implanted in the tissues of the Fallopian tube has been advanced as an etiological factor in the development of an ectopic pregnancy and even to account for the rupture through the wall of the tube. There is, however, very little evidence to substantiate this beautiful theory, as were this the case a similar corroding process would logically take place when the ovum is lodged in the uterine cavity. If it is possible for the ovum so to push itself through the wall of the Fallopian tube, why should it not corrode its way through the uterine wall? It appears to me that wherever the ovum is lodged and fertilized it is simply a question of obstruction to its descent and its external expulsion through the os uteri externum, whether the ovum remains lodged in its own Graafian follicle, in the Fallopian tube, or in the uterine cavity and here lays the foundation for an ovarian, tubal, or a normal uterine pregnancy. In most instances the ovum is simply impeded in its descent in the uterine cavity and remains confined in one or the other cornu owing to the hypertrophy of the mucosa with the decidual reaction that takes place coincident with the liberation and fertilization of the ovum. Its attachment and retention in the tube or in the cornu of the uterus is simply one of union of surfaces of living tissues, a parasitic invasion, so to speak, the fertilized ovum receiving its supply of nutriment from the new host and by the formation of chorionic villi and a decidua proceeding toward the development of the fœtus and its membranes.

The implantation of the ovum within the uterine cornu would explain the so-called gibbous condition of the uterus in normal pregnancies to which Dickenson and Howard Kelly have referred. Thus one cornu of the uterus, in the early stages of pregnancy, projects above that of the opposite side forming a more or less distinct tumor at this point. The protruding cornu is generally softer in consistency than the other one.

Kelly says he has been able to verify this observation of Dickenson in many instances. I have also observed this inequality in size and consistency of the cornua in several cases of pregnancy but have not been able to elicit it after the third month. Kelly remarks that it is "as though the ovum had lodged and were developing in but one horn." I am inclined to believe that as a rule the fertilized ovum becomes imprisoned at this point, its further descent and escape being thereby rendered impossible for a time. When the ovum or embryo is implanted in one of the false diverticula in the tube, as described above, and especially in one which is rather superficially placed, it is easy to understand the early extrusion of the ovum through the wall of the tube and in the direction of least resistance or outward from the lumen of the tube. It is possible to have a very early rupture of the tubal wall in such cases without alarming symptoms or much injury to the tubal wall.

A tubal rupture and a tubal abortion seem to be dependent upon the site of implantation of the ovum along the Fallopian tube — the nearer the ovum approaches the uterine cornu the greater is the liability to rupture and the less the tendency to extrusion through the cœlomic ostium.

In all the specimens I have microscopically examined from the gynecological service of Lakeside Hospital, a bilateral inflammatory reaction has preceded the development of the ectopic gestation. The histopathological changes within the structure of the tube were too advanced to have occurred subsequently even where there had been a history (as happened in two of our cases) of a tubal rupture occurring one month previous to removal of the diseased structures. In every case, even in those in which a surrounding inflammation was very limited in extent, as evidenced by the presence of adhesions and by the general macroscopic appearance of the tubes, an existing inflammation or evidence of a pre-existent reaction could be demonstrated. In some there was a difference in degree in the extent of the inflammation, while in others a healed condition of the tube was to be seen. In no case had the inflammation been acute, but several showed a subacute or a so-called chronic process. Other tubes revealed an entirely healed condition of the tube, the anatomical changes that remained being the sole indications of the pre-existence of an inflammation.

Without exception, then, we found reliable evidences that an inflammation had accompanied or preceded the ectopic condition. Where both Fallopian tubes had been removed, the same appearances were noted in each excepting the changes in the one incident to the presence of the ovum and a slight difference in degree of the inflammatory reaction.

The tubes in every case showed subacute or chronic adhesions. The muscularis showed a diminution in the amount of muscle tissue, this having been sacrificed in part and replaced by connective tissue. In most of the cases, therefore, the tubal wall in the non-implicated, non-pregnant tube was noticeably thickened. However, in the tubes in which complete healing had occurred the tube wall, although it contained a diminished amount of muscle tissue with a relative increase of connective tissue, was not appreciably thickened. This fact, of course, is explained by the contraction of the connective tissue fibers which limits its vascularity, which regulates its formation. In the specimen showing an inflammatory reaction in the impregnated tube, or in the opposite tube when it was removed, the tubal wall was more or less infiltrated with small round cells, which always predominated, polynuclear, plasma, and eosinophilic cells were also present.

In only two cases was free pus present in the lumen of the tube and then only in very small quantity. Some of the ovaries removed, in addition to the external adhesions, including beneath them the germinal epithelium of the surface of the ovary, presented further evidences of an inflammatory reaction in their parenchyma. The tissue in some was very dense and somewhat altered in character from the normal type. At times, however, it was difficult to distinguish the newly-formed connective tissue in healed areas in a previously inflamed ovary from the original stroma. On this account it is possible to overlook many cases in which an inflammation has at some time been present in the ovary.

In several cases a large recent or fairly recent cellular corpus luteum was demonstrable, but in others the corpus luteum had degenerated to form a cyst or the lutein cells had become replaced by fibrous tissue to form the so-called corpus fibrosum or corpus albicans (in the gross). Some of these were no doubt the results of a previous ovulation. Except in an occasional rare case in which the etiology is apparent, no one can say with certainty just what lesion, or combination of lesions, is responsible for the development of an ectopic pregnancy. It seems to me, however, that we must associate this condition with the most common lesion with which the tube is involved, as well as the opposite one, and one that is capable of obstructing and preventing the entrance of the ovum into the uterine cavity. Seldom does one find the cornual extremity of the tube occluded and thus is it possible for the spermatozoa to gain admission into the main lumen of the one or the other tube. If the uterine end of one tube were occluded and that end of the opposite one patent, the spermatozoa could enter the open one, advance along the length of the lumen and after an intrapelvic excursion, enter through the abdominal ostium of the opposite Fallopian tube to fertilize the ovum, whether its progress is blocked by its lodgment in a false diverticulum, by the simple occlusion of the uterine portion of the tube, by a polyp, or by the calcified remains of a fœtus, as occurred in a case operated upon by H. C. Coe and reported by J. W. Williams. This case showed an occlusion of the cornual end of the left tube which lodged two extrauterine pregnancies. It also demonstrated the external migration of the ovum (the corpus luteum being found in the right ovary) and also that the spermatozoa had entered the peritoneal cavity before reaching and fertilizing the ovum.

Actively motile spermatozoa have been seen spread out over the surface of an ovary and in the peritoneal cavity. The liberated ovum is seldom, if ever, inaccessible to the motile spermatozoa, providing of course that the uterine end of the tubal canal is open and that their exit from the tube into the peritoneal cavity is possible whether that occurs through the normal abdominal ostium or through the lumen of an accessory Fallopian tube situated anywhere along its length. Thus an ovum, lodged in a diverticulum — which is simply an offshoot from the main lumen of the tube, generally branching off at an acute angle or running parallel with it — can be found and fertilized by the spermatozoa. We have demonstrated, as have also J. W. Williams and others, that cilia are always present in part and in addition that a portion of the bundles of the unstriped muscle tissue is always preserved. Peristaltic movements of the tube are thus possible.

Flexions are seldom so acute or marked that they would not straighten out under peristaltic action sufficiently to allow the ovum to pass. In flexions of the tubes examined histologically no perceptible atrophy of their wall nor stenosis of their lumen could be demonstrated at the site of the flexion.

Accessory Fallopian tubes are relatively rare. During my term of service as resident gynecologist we have had only 4 instances in a total of nearly 350 cases in which these existed. In no case of ectopic pregnancy were they demonstrable in either the pregnant tube or in the one on the opposite side.

Fibromyomata and polypi of the tube are exceedingly rare and we have failed to note a single instance of either. They are, we believe, of minimum etiological importance.

In external migration of the ovum there is no evidence to substantiate the assertion or the theory that delay in the entrance of or the augmented size of the fertilized ovum precludes its passage along the canal of the tube. The distance traversed by the ovum might be very short since the tube on one side has at times been found quite close to the ovary of the opposite side. Indeed it is probable that oftentimes in external migration, the opposite tubal ostium has been closer and more accessible to the liberated ovum than the tubal ostium of the same side. Other factors may influence the extratubal transpelvic route of the ovum.

After a review of the literature upon the etiology of ectopic gestation and a study of the pathological conditions associated with it both from a clinical and a histological standpoint, we are led to conclude that the formation of false diverticula, resulting from a salpingitis, is the most constant anatomical change or lesion found in the Fallopian tube capable of impeding the descent of the ovum and producing a tubal pregnancy. Personally I would venture the assertion that at least 95 to 98 per cent of these cases have their origin in this manner.

SUMMARY

1. A histological examination of the implicated (as well as the non-implicated) Fallopian tube in cases of ectopic gestation is of more value in explanation of the etiological factor or factors than simple clinical observation.

2. Clinical examination of the structures may reveal no evidence of an inflammatory reaction nor of anatomical malformations which, however, are possible of demonstration by microscopic examination.

3. Microscopic examination may show no adhesions sur-

rounding the Fallopian tubes, whereas, microscopically, the mucosa and muscularis of the same tubes may show the evidences of a pre-existent inflammatory reaction.

4. In all our specimens evidences of an inflammatory reaction, which had preceded the onset of the ectopic gestation, were demonstrable. The observations of Opitz in a series of 23 cases coincide with our own.

5. Schauta, Küstner, Dührssen and others believe that predisposition to a tubal pregnancy depends upon a previous inflammation in the tubes and that in most cases it is due to a gonorrhœal infection. With these conclusions I am certainly in accord.

6. An infection of the gonococcus of Neisser more than any other kind of infection predisposes to the formation of the false diverticula. A tuberculous process does not produce the ideal conditions for the retention and especially for the development of an ovum in the tube.

7. The inflammatory changes in all cases in which both tubes were removed were shown microscopically to be bilateral, and diverticula were present not only in the tube which lodged the ovum but also in the opposite one.

8. The statistics of cases of tubal pregnancy occurring so frequently in the opposite Fallopian tube a few months to a year or more after an operation for the removal of one on the other side would warrant us in advising the patient that the retention of the apparently sound or slightly diseased tube may possibly lead to the development of another ectopic pregnancy.

9. Before saving of the opposite tube for the purposes of conception in the uterus, which I favor if the tube is not hopelessly occluded or too densely adherent, I should always warn the patient of the danger of another ectopic gestation. If the patient or her friends assume the responsibility, the tube, if capable of functioning, or if the occlusion or other pathological lesions can be corrected, should be conserved. Otherwise I advise its removal.

10. With the development of false diverticula or mucous-lined channels such as were histologically demonstrable in our series of cases and in that of Opitz the chances for an ectopic gestation as against a normal uterine pregnancy are in the proportion of from 2 to 8 to 1.

11. In a routine examination of many thousands of specimens I have noted the presence of true anatomical diverticula in a few instances. The other possible factors ascribed as etiological factors are many times rarer than the cases of ectopic pregnancy.

12. From an exhaustive study of the subject and from the analysis of a series of cases we believe that the presence of these false mucous-lined channels or diverticula produced by an inflammatory reaction in the tubes is the chief predisposing cause of tubal pregnancy in at least 95 to 98 per cent of all cases.

PART II.

PATHOLOGICAL AND EXPERIMENTAL PAPERS.

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Western Reserve University
Department of Surgery

CLINICAL AND EXPERIMENTAL OBSERVATIONS ON SURGICAL HEMORRHAGE

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A SERIES of experiments on sixty-one animals was made with special reference to arterial hemorrhage. In the experiments in which the animals were rapidly bled, the blood-pressure fell more evenly than in the experiments in which the animals were slowly bled. In rapid bleeding, the blood-pressure continues to fall after the cessation of the hemorrhage. In all varieties of hemorrhage there is an immediate tendency to a compensatory recovery. The extent of the recovery depends upon the individuality of the animal and amount of the hemorrhage.

Roughly speaking, compensation is noted in all the grades of hemorrhage until such a degree has been reached that the vasomotor center is no longer actively responsive to reflex stimulation, such as burning of the paw or stimulation of the sciatic nerve. With the hemorrhage and the fall in the blood-pressure, the specific gravity of the blood falls. After the hemorrhage has proceeded until there is no effort at compensation, the animal rarely recovers unaided. If, however, the blood-pressure was raised either by saline infusion, by bandaging, or by the administration of adrenalin, sometimes the centers became more active, and the blood-pressure assumed and held a higher level.

In the experiments in which the hemorrhage was continued until there was no spontaneous compensation, and there was no response to reflex stimulation, the animal rarely could be made to recover. There was a marked difference, however, in the final result if an interval were allowed between the time of the ending of the hemorrhage and the beginning of treatment. The longer the interval of low blood-pressure without spontaneous compensation, the less marked were the effects of the stimulation of the vasomotor center, or other methods of treatment.

The proportion of lost blood to the body weight that animals withstood and recovered from varied considerably in individual cases. This degree of variation seemed to us to be greater than is usually given. In some animals, recovery occurred when six tenths of the estimated blood had been lost, while in others death would occur after four tenths. It was impossible to estimate, in any given animal, with any degree of accuracy the proportion of blood to its body weight it might lose and recover. What, then, are the factors entering into the fall in the blood-pressure and its recovery? It may be assumed that the primary factor is anæmia, thereby lessening the immediate nutritin of the active physiological mechanism for the maintenance of the normal blood-pressure.

Of these factors, we may assume that the vasomotor center stands first. We may further grant that the exosmosis from the tissues into the vascular system is also a factor. That the vasomotor center is a most important factor is shown by the following.

1. When an animal was bled very considerably, even to a dangerous degree, and there was still some natural compensation, though amounting to only a few millimeters of mercury, and this animal was then given a therapeutic dose of strychnine, the blood-pressure was usually considerably raised over a short period of time. Since this rise in the blood-pressure as a result of the physiological dose of strychnine is known to be due to a stimulation of the vasomotor center, we may, then, conclude that could the vasomotor center have a spontaneous stimulation, or an automatic stimulation equal to that of strychnine, and should this stimulation of this center be continued, the animal would make a prompt and effective recovery from such degree of hemorrhage. On the other hand, if no strychnine is given in such a case, the blood-pressure is likely to remain at or near the level of the first compensation, and after a period of time, and inversely with the lapse of time, the effect of a later stimulation is less marked.

This is to say, it would seem that the vasomotor center becomes less active on account of a continued anæmia.

2. In animals in which the vasomotor center has been previously impaired by shock, the compensation after hemorrhage is less marked, and its response to vasomotor stimulations likewise less.

3. In animals in which all the centers are greatly reduced by reason of malnutrition or disease, compensation is less marked.

4. Negatively, in a hemorrhage experiment the heart itself is unable materially to affect the blood-pressure, because it has been shown that the rate and force of the heart's contraction have but a limited range in their power to raise the blood-pressure under any and all circumstances.

It may, too, add to the support of the vasomotor factor to note that if a large dose of adrenalin is added to the circulation even after death, and the heart's action is instituted by manual pressure, the blood-pressure still may rise. That is to say, the question of compensation (hence, recovery after hemorrhage) is very largely one of dynamics, and concerns primarily the vasomotor center. Since it is noted that the addition of any fluid to the circulation in the lower, though not the lowest, states of the blood-pressure causes a rise in the pressure, we must grant that the addition of fluid from the extravascular tissues of the animal itself must, on the grounds of analogy, play its part, though it be a minor one. The specific gravity of the blood, the hæmoglobin determination, and the red-blood count, all show very marked variations in the different experiments and in the various parts of the same experiment. The first effect noted upon the respiration in the primary arterial hemorrhage is an increase.

On the Effects of Certain Drugs in Hemorrhage. The effect of drugs varies in the different parts of the circulatory apparatus in the various degrees of arterial hemorrhage. They not only showed these distinctions, but also presented a marked difference in their effects in the various periods of time after the hemorrhage at which they were administered.

Strychnine. The effect of strychnine immediately given in the various degrees of arterial hemorrhage diminished as the hemorrhage increased. After a slight hemorrhage, the blood-pressure was raised almost as much as in the control dog. In profound hemorrhage, in a few instances no effect on the blood-pressure was noted. When the therapeutic doses of strychnine were repeated in the cases in which there was a distinct effect upon the blood-pressure, the effect of the second dose was usually less marked than that of the first, and sometimes no effect whatever was noted. However, in all the instances of profound hemorrhage, the longer the interval between the hemorrhage and the administration of strychnine, generally speaking, the less marked was the effect of strychnine upon the blood-pressure. If, however, there was still left some compensatory power in a profound hemorrhage, and the blood-pressure was first raised as much as possible by saline infusion, the effect of strychnine was then more marked.

Heart. The effect of strychnine upon the heart was more marked in the case of deep hemorrhage than with the control dogs. Its apparent effect upon the heart, however, in any of the experiments, excepting those in which a large hemorrhage had been produced, was not marked.

Digitalis. What has been said as to the effect of strychnine upon the vasomotor center may be said of digitalis, although in the case of digitalis there was markedly greater uncertainty and irregularity in the results.

Heart. The effect of digitalis upon the heart showed a more distinct difference. The deeper the hemorrhage, the lower the blood-pressure, the more marked were the effects upon the heart; these effects being an alteration in the rhythm and the frequency of the heart-beats, and in many cases sudden cardiac failure. The action on the heart was more constant than the action on the vasomotor center.

Saline Infusion. In the vast majority of the experiments, saline infusion was followed by an immediate rise in the blood-pressure, with an increase in the pulse volume and the output of the heart, as indicated by an increased length of the stroke of the writing style. In the experiments, however, in which the blood-pressure was reduced so low that no natural compensation was noted, occasionally it was found that there was no rise in the mean blood-pressure on administering saline infusion. The increase in the output of the heart and in the pulse volume, at the same time, was markedly increased. In the majority of instances in the various degrees of hemorrhage above the latter, the effect of saline solution was that of raising the blood-pressure. However, in the cases in which the saline infusion was given rapidly, the highest point first obtained was usually not maintained. In some instances the blood-pressure would continue to rise after cessation of the saline infusion, and the general condition of the animal was markedly improved, but in other instances, especially those in which hemorrhage was profound, the saline infusion caused extreme embarrassment of the heart action, even a fatal dilatation. We may then consider the effect of the saline infusion under the headings: 1. Its effect upon the vasomotor center; and 2. Its effect upon the heart.

1. *The Vasomotor Center.* For the most part, the vasomotor centers seem to be favorably influenced by the increased blood-pressure and increased circulation established by the infusion. There were instances where, even though there was no increase in the vasomotor action, it at least held its own at a higher level; then, again, it was sometimes noted that after a saline rise in blood-pressure, burning the paw elicited a greater activity of the vasomotor center than was noted before. In these cases, too, the administration of strychnine caused a more marked effect upon the vasomotor center. That is to say, it seemed that the increased circulation through the vasomotor center by means of the saline infusion brought back renewed activity of this center. There were no cases in which it was clearly observed that saline infusion affected the vasomotor center especially unfavorably.

Heart. While in the case of the vasomotor center the effect of saline solution was either to improve it, or at least not to damage it, in the case of the heart the same results were not always noted. In certain instances, especially when the infusion was given rapidly, an acute, sometimes fatal, dilatation of the heart was noted. Many times the heart was greatly embarrassed, though it finally recovered. It is well here to call attention to the fact that the work of the heart when the volume of fluid is augmented is increased in a geometric ratio. That is to say, if twice the amount of fluid were suddenly thrown into the heart, its work would be increased fourfold. It was found more effective to give a guarded infusion at first, noting the effect upon the heart, then gradually increasing as the heart itself became able to assume more work. Substitution of oxygenated Locke's solution for normal saline seemed, on the whole, to act better.

Effect of Saline on Other Tissues. When the saline infusion was given continuously in rather too large amount, it was rapidly transferred to the splanchnic area, escaping through the vessels here, filling the walls of the hollow viscera, and even escaping into them. The effect, then, of saline infusion is limited to such effect as it may have in its transit through the circulatory apparatus. The effect of saline infusion in respect to the heart and the vasomotor center, as in the case of strychnine and digitalis, depended somewhat upon the length of time that elapsed before the ending of the hemorrhage and the beginning of the infusion. The later the infusion, the less favorable was the effect of the solution.

Mechanical Means of Treatment. Bandaging the extremities and the trunk raised the pressure and maintained it though the rise was not large, and no unfavorable effects were noted.

The red cells and other formed elements of the blood reform with great rapidity. For example, in an animal with a normal of 5,000,000 of red cells the count had fallen to 1,500,000, but within a week the normal number was regained. The specific gravity of the blood first fell, then rose rapidly. This rise was noted almost immediately after the greatest depth of its fall. Marked waves, not only in the specific gravity, but also in the blood count, were noted.

Oxygen. The favorable effect of oxygen inhalation during the critical stages of hemorrhage was in almost every instance well marked.

Recent researches, the details of which will soon be published, have established a method of treating hemorrhage which promises to be extraordinarily effective. It consists of making an end-to-end anastamosis between an artery of a donor and any vessel of the donee. In this manner the lost blood, or a sufficient part of it, may be readily transferred. The treatment seems to be absolutely effective, even after the respiration and the circulation have ceased.

HEMORRHAGE IN OPERATIONS

It is always well to bear in mind, in estimating the effect of hemorrhage in a strong subject in an operation, that from two to three per cent of the body weight may be lost in hemorrhage without materially changing the blood-pressure; that the blood-pressure is thus maintained at the expense of an increased action of the vascular nerve mechanism; that such a patient, despite the apparent good circulation and well-sustained pulse, cannot withstand shock or other depressing factors as well as a patient having a similar pressure, but who has lost no blood. It is well, too, to remember that a rapid arterial hemorrhage, causing a more sudden anæmia of the bulbar centers, incites a marked stimulation of these centers, tending to bring about a recovery of the blood-pressure. On the other hand, a slow venous or capillary hemorrhage does not cause this sudden anæmia; it more directly deprives the heart of blood, and is therefore attended by a more considerable fall of the blood-pressure. The conservation of blood in any surgical operation is a matter of supreme importance.

It is, we believe, a good rule to operate only in a dry field, picking up all vessels as they bleed, or, if possible, before their division, and finally tying them. For, although at the end of an operation, when the blood-pressure has been depressed, when one removes the clamps, but few vessels may actively bleed, yet with the rebound of the circulation, especially during vomiting, when there is a marked increase in the venous pressure, oozing is quite sure to occur.

In amputations, resections, etc., the method of plain dissection has been employed in the past few years in most instances; that is to say, an amputation of the thigh is done by precisely the same rules of dissection as an amputation of the breast. It is true that with a tourniquet less blood is lost during the division of the tissues, but the total amount finally lost during the first twenty-four hours, by applying the methods of plain dissection to these operations, has certainly been lessened. Not only is the total amount of blood lost less, but in the case of the Esmarch tourniquet on account of the temporary vasomotor paralysis, oozing continues a considerable time after the operation has been completed. That is to say, there is quite certain to be oozing after the patient has been reduced by shock and can least afford any additional depressing factors. The first twenty-four hours are likely to pass more evenly following a plain dissection than by tourniquet.

In the heavier operations of the neck, face, and head, a method, previously described, of temporarily closing the large arteries by means of a special clamp has been used. This has been applied 61 times among 680 operations in this region. No ill results have been noted. The ages varied from 9 months to 79 years. The common carotid artery is so readily exposed, provided one disregards the teachings of anatomists, and merely makes an intermuscular division of the sternomastoid and picks up the artery, that it adds but little to the operative technique. The closure of this artery does not entirely control even the arterial hemorrhage of the region supplied, on account of the rich anastomosis of both the external and internal carotids. We have seen, for example, in elderly subjects with atheromatous vessels and a high blood-pressure, a distinct recurrent pulse in the branches of the external carotid artery when the common was totally closed by the clamp. The opposite artery supplied such a volume of blood under high tension to the brain, that a pulse wave extended through the periphery in the brain back to the internal carotid to the bifurcation of the common, then up the external carotid into its terminal branches, thus giving a pulsating circulation from the opposite side and from the periphery. This, however, is quite unusual. It is obvious that in such a case as this it would be more effective to close the external carotid, rather than the common. The closure of both external carotids would naturally entirely control the arterial hemorrhage. Both common carotids have been closed in several instances. It is interesting to note in these that the patients required but little anæsthetic. If one should do this, it is quite important to keep a close observation upon the respiration, as it is more affected than the circulation. We have not found that closure of the common carotid artery is of any special advantage in those brain operations in which the principal risk of hemorrhage is from the venous circulation. We usually close the common carotids in the operations for excision of the Gasserian ganglion, because it so much minimizes the hemorrhage in dividing the heavy, soft tissues encountered in this operation, as well as the blood-supply of the diploë and the coverings of the brain. After this stage of the operation is passed, closure has no longer any influence upon hemorrhage, because the remainder of the hemorrhage is almost wholly venous. The venous hemorrhage is greatly minimized by the inclined head-up posture with the pneumatic suit. Closure of the common carotid has been strikingly helpful in aneurysms of the various portions of the scalp, skull, or orbit. Recently, in an operation upon a large bulging tumor, protruding through a former osteoplastic operation on the skull, the hemorrhage was better controlled by the application of rubber dam applied as a close-fitting turban, and then making the incision through the rubber dam in a quite bloodless field. The rubber dam turban has since been used in securing anæmia of the skull in other operations.

In operations in the oral cavity, such as cleft palate, excision of the tongue, jaw, etc., the anæsthetic is given at a distance from the patient by means of rubber tubes placed through the nares, according to a method mentioned in the *Annals of Surgery* several years ago, and more fully described in another paper in this number.[1] By this method a continuous, even anæsthetic may be maintained, not a drop of blood can be inhaled, the anæsthetizer is entirely away from the field of operation, and one is as free to execute in an unhampered way the technique as in herniotomy. Not only are certain dangers and inconveniences obviated, but in case of cleft palate operations, for example, one may easily pack a large piece of gauze firmly against the palatine artery, quite effectively controlling the hemorrhage. In partial excision of the tongue the pharyngeal packing may be so arranged as practically to close the supplying arteries, effectively controlling the hemorrhage. We have noted in cleft palate operations the absence of the febrile rise and other symptoms of sapræmia which so frequently followed the former technique. There is no simple procedure in our experience that has yielded such splendid results as the intubation of the pharynx in operations in the oral cavity.

In tumors of the neck, in all suitable cases the artery is temporarily closed. In addition, if there is an unusual risk of hemorrhage, the patient is also incased in a rubber pneumatic suit and placed in a 45° upright posture. In this way, by taking advantage of gravity, the large venous trunks are emptied of their blood, and a splendid anæmia is obtained. One need only note the fading out of the superficial vessels as the upright posture is assumed to appreciate how much the hemorrhage is minimized. With the arterial hemorrhage very largely controlled by the closed artery, and the venous hemorrhage minimized by posture, one is able without difficulty to keep a dry anatomical field for the clean dissection of any portion of the neck. The object of the rubber suit, of course, is that of assuring ourselves, in case there is some failure of the vasomotor center, of a safe amount of blood in circulation in the thorax and the brain by preventing its accumulation in the lower extremities and the abdomen.

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[1] Referring to paper on "Technique of Tubation of Pharynx in Face and Neck Operations," by J. H. McHenry, M. D.

In the first interscalpulo-thoracic amputation there was applied the technique later employed and published by Cobb, Lund, and Cushing; namely, that of making an incision over the clavicle, blocking the brachial plexus with cocaine to prevent shock, then tying off both the artery and the vein preliminary to the technique of amputation. In this case it was surprising to find a large amount of blood had accumulated in all the vessels of the arm and shoulder through the collateral anastomosing vessels, and whereas there was but little loss of blood from the operation itself, there was an unnecessary loss of blood in the distended vessels of the shoulder and of the arm. In the next case the device suggested by Cobb of Boston was employed, of pressing the blood out of the arm and putting a tourniquet around the arm for the purpose of preventing the influx of blood into the otherwise empty vessels.

SECONDARY HEMORRHAGE

In a personal experience of more than six thousand major operations, there have been very few cases of secondary hemorrhage. Among these were two following operations for acute suppurative appendicitis. In one case there were repeated hemorrhages, the first appearing ten days after the operation, the last and fatal one, eighteen days later. In this case the major portion of the blood passed into the intestine as a concealed hemorrhage.

Another case of fatal secondary hemorrhage occurred in the wound made by an incision to open an extensive abscess of the neck following diphtheria. In this case the child was extremely reduced, was pale and septic. The hemorrhage came from many small vessels in all the parts of the abscess cavity—a general oozing which could only be controlled by ligature of the common carotid artery. The child died later, of infection.

Another case of secondary hemorrhage followed a misjudged operation for carcinoma of the lower jaw and glands of the neck, in which it was found practically inoperable. The hemorrhage came on the eight day after the operation, and was controlled by ligation of the common carotid under cocaine, and was followed by recovery.

Among 121 operations upon the biliary passages, there were encountered two instances of hemorrhage from the gall-bladder, the hemorrhage consisting in an oozing from its mucous membrane, continuing at intervals, in the one case, of seven days, and in the other, of twelve days, and finally ending in recovery.

As several of the masters in the surgery of this region have pointed out, when there are petechial hemorrhages in the presence of jaundice, the risk of hemorrhage is too great to warrant any operative procedure. In our clinic we have, in all cases of jaundice, or of long-continued gall-bladder disease with intermitting jaundice, made preliminary coagulation time tests, and if the coagulation time was ten minutes or more, no operation was advised. In both of the cases of secondary hemorrhage above mentioned, the coagulation time was six minutes or under.

In the treatment we have depended upon local measures, such as packing, and the administration of calcium chloride in from forty to sixty grain doses, given by the mouth, by the rectum, or subcutaneously, according to circumstances. In the cases in which this drug was given prior to an operation, where coagulation time was rather too long, it was noted that it required the administration in large doses over a number of days before the coagulation of the blood is materially changed. We have but little reason to believe that calcium chloride is an effective remedy in an immediate emergency. There has not been noted any hemorrhage from other tissues than the mucous membrane of the gall-bladder, and should an instance of severe hemorrhage be encountered again, a cholecystectomy would probably be employed after the failure of the more common remedies. We have not yet seen a single instance of secondary hemorrhage in an aseptic wound excepting in the case of hæmophilia.

TREATMENT

The arrest of hemorrhage is so largely a matter of technique, and in almost every instance is so specialized by location and circumstances, that we shall not omit it, and shall briefly consider the immediate general treatment of acute hemorrhage.

The problem resolves itself into the temporary application of the most effective measures of preventing a fatal anæmia of the heart and the brain. These measures naturally fall into two classes: 1. Therapeutic; 2. Mechanical.

Among the therapeutic measures, morphine to secure rest is frequently important. Among the stimulants, strychnine is important, but in the serious cases it should be cautiously given. Its effect is heightened by first raising the blood-pressure by the infusion of saline or Locke's solution. In great urgency, it may be administered slowly in this solution. Digitalis, like strychnine, is least beneficial when most needed. If sufficient dosage be administered to effect the vasomotor system, the heart may be fatally overstimulated. Adrenalin has a remarkable effect upon the blood-pressure, but its effects are fleeting. A sudden cardiac break-down may unexpectedly occur.

Among the mechanical measures, normal saline or Locke's solution is perhaps most important. In intravenous infusion in the anæmic heart, it is imperative to bear in mind the possibility, or, may we not add, the probability, of an acute dilatation of the heart. When the pulse shows a large wave, with but little resistance and a markedly slowed rhythm, great caution is necessary. It must also be borne in mind that the blood does not tolerate much dilution; that excessive saline passes rapidly through the vessel-walls, accumulating in the splanchnic area and in the pleural cavity and the lungs.

Posture is a measure of self-evident value, and cannot well be overestimated. Conversely, change from the head-down position involves great risks. Not only cerebral anæmia, but sudden heart failure may follow.

Bandaging the extremities and the abdomen over heavy layers of cotton is an effective aid; even more effective is the application of the pneumatic rubber suit.

Artificial heat, so applied as not seriously to disturb the patient, or to interfere with more important measures, should be employed.

In profound hemorrhage in which the number of red cells are so greatly reduced as seriously to decrease the amount of oxygen carried to the vital centers, the administration of oxygen is a most effective remedy. Indeed, there is a stage of hemorrhage characterized by such a degree of suboxidation that the arterial blood assumes a peculiar port-wine hue in which recovery is not possible without the freest inhalation of oxygen.

Illustrative of the value of mechanical pressure, a cut-throat patient was admitted to the wards of Lakeside Hospital, exsanguinated and pulseless. Saline infusion and stimulants had been given in maximum amounts during twelve hours, but the circulation always relapsed, and at the time of application of the rubber suit the pulse was barely perceptible, the respiration gasping, and the patient was unconscious. On applying firm pneumatic pressure up to the costal borders, the pulse became immediately better, the blood-pressure rising to 110 mm. mercury, and consciousness was regained. The suit was worn during twelve hours, when her condition had sufficiently improved to warrant a gradual decompression. Recovery followed.

The management of a recent case is illustrative of our conception of meeting a crisis in hemorrhage.

A delicate ten-year-old girl, with very extensive tubercular glands in both sides of the neck and extending into the thorax, was first subjected to excision on one side, and later on the other. In the course of the latter, the glands were firmly adherent, and extended well down below the clavicle and the sternum. While separating with difficulty the last large gland with the forefinger, there was a large gush of arterial blood from a lacerated subclavian artery whose wall had become pathological from the closely adherent infected gland. The wound was at once firmly packed, and a massive pyramid of gauze was applied under pressure.

At the end of seven days the hemorrhage was renewed and the patient became quite exsanguinated.

The bleeding was then temporarily controlled by pressure, while preparation was made for ligating the innominate artery. A full therapeutic dose of morphia was given, the lower extremities and the abdomen were covered with heavy layers of cotton batting and firmly bandaged. After the morphia had reached the maximum effect, she was cautiously anæsthetized, an assistant gave simultaneously in the median vein a saline infusion at the rate of 3 c.c. per minute, and more rapidly during the rapid hemorrhage during the exposure of the artery. The innominate was then ligated below the vertebræ, collateral circulation returned 12 hours later, and the child made a good recovery.

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AN EXPERIMENTAL RESEARCH INTO THE RESUSCITATION OF DOGS KILLED BY ANESTHETICS AND ASPHYXIA.

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PLATES XLII–XLIX.

In a previous communication by one of us (Crile) resuscitation was attempted by means of both direct and indirect cardiac massage, with and without artificial respiration, with and without intravenous saline infusion, and with and without the addition of adrenalin. The results of these experiments may be summarized as follows: By cardiac massage alone animals were rarely resuscitated at any time after quiescence of the circulation and respiration; by combining either direct or indirect cardiac massage with artificial respiration and the head-down posture a certain percentage of the animals were recovered after the lapse of from one to three minutes. The results, however, were quite uncertain, and in the case of death from chloroform recovery was the exception. By adding to cardiac massage artificial respiration and intravenous saline infusion, resuscitations were in a slightly greater proportion successful. The same procedures, with the addition of adrenalin to the intravenous saline infusion, were markedly more successful in the deaths from asphyxia through rarely so in the cases of death from chloroform. It required in almost every instance a vigorous compression of the thorax over the heart for a considerable time, varying from five to ten minutes, before resuscitation could be accomplished. Even then there were a considerable number of failures. In the majority of these failures autopsy showed the heart to be in a state of marked distension, indicating complete cardiac paralysis; not infrequently when results were delayed, the acute cardiac dilatation was partly relieved by venesection and by placing the dog in the inclined head-up posture, thereby partly relieving the paralyzed heart of its over-distension.

In this research the problem was approached from the arterial side, with the following physiologic factors as a basis: The physiological researches of Ringer, Kuliabio, Sollman, and others had shown that the excised heart could be made to beat again, even many hours after excision, when the coronary arteries were subjected to a considerable pressure from some circulating medium. The researches of Sollman showed that the *inauguration* of the beat was more dependent upon the physical factor of the increased pressure in the coronary arteries than upon the quality of fluid producing such pressure. He was able to inaugurate cardiac beats by perfusing the coronaries with metallic mercury. The basic problem, then, in resuscitation seemed to us to be that of securing by means of some infusion a coronary pressure approximately amounting to from thirty to forty millimeters of mercury. It was impossible to raise the coronary pressure in the intact animal to this height by means of cardiac massage alone; it was almost impossible to raise it by the mechanics of infusion alone, and generally impossible to raise it to this height by means of cardiac massage and plain infusion combined.

The value of adrenalin in raising the blood pressure, by its action upon the vascular walls in the state of suspended animation, has been heretofore thoroughly established. Introducing the adrenalin into the venous circulation, while easy and practical, had the following disadvantage: the adrenalin first came in contact with the vessels having the least power of influencing the blood pressure, and before a material rise could be effected by its action upon the arteries it was necessary that the solution should pass through the right heart, the lungs, then back to the left heart on its way to the aorta, thence affecting directly the coronary artery. In the previous research it was found that this too often caused an accumulation of solution and blood in the dilated, paralyzed chambers of the heart, defeating resuscitation.

It seemed reasonable to us to suppose that the most direct and effective way of producing a coronary pressure amounting to thirty or forty millimeters of mercury was by introducing a solution of adrenalin into the arterial system toward the heart. In this way the moment the adrenalin was introduced it caused a contraction of the strong arterial walls, beginning to produce an arterial pressure which would communicate directly with the coronary artery without first passing through the already distended and paralyzed chambers of the heart and through the lungs. These considerations were particularly impressed upon us by a clinical case which has elsewhere been reported.

Sixty experiments were made in which the tracings were preserved and the records noted. In the recovery experiments the greatest care was taken to secure for the animals all the comfort possible, and as few of this class of experiments were made as was consistent with the collection of data sufficient for our conclusions.

Three groups of cases were investigated: (1) death from asphyxia, (2) from ether, (3) from chloroform. Inasmuch as the methods and results were quite similar, they may all be described together.

We first tested the method as to its usefulness in raising the blood pressure, and found that by tying a cannula into an artery toward the heart and introducing through it a solution of adrenalin the blood pressure was immediately raised, the latent period being distinctly less than when the solution was introduced intravenously. In fact, we may say that there was no latent period, the blood pressure rising instantly. It was found, too, that the most effective method of raising the blood pressure was by the injection of the full strength of 1–1000 solution of adrenalin by means of a hypodermic syringe into the rubber tubing near the cannula. The results in these experiments showed a distinctly more powerful action than in the experiments in which the solution of adrenalin was previously made and poured into the funnel.

The first experiment was made upon an animal killed by chloroform. A cannula was inserted in the femoral artery directed toward the heart. After two minutes artificial respirations were begun and the saline solution was allowed to flow for perhaps ten seconds; then a hypodermic injection of from one to two ubic centimeters of 1–1000 solution of adrenalin was given into the tube near the cannula. A few seconds later the blood pressure began to rise steadily; then a few firm pressures upon the thorax over the heart caused a leaping up of high pulse waves, and at the end of three quarters of a minute the heart beat vigorously, driving the blood up into the infusion bottle, which was raised to a height of five feet. The saline injection and cardiac massage were discontinued, and in a few minutes irregular respirations slowly began, decreasing in force and increasing in frequency until the normal was established. The animal was then killed.

Following this experiment others were made, each time a longer period being allowed to elapse from the moment of death until the beginning of resuscitation. In determining the moment of death from chloroform it was found that by administering an excessive dose by inhalation the blood pressure sank with remarkable rapidity to the abscissa line, but that after this in forty per cent. of such deaths feeble pulse waves reappeared after periods varying from a few seconds to over three minutes, the blood pressure rising to from ten to thirty millimeters, then gradually declining, the pulse wave progressively diminishing in length. After a period of resumption of beat varying from a few seconds to six minutes, and averaging two minutes, the pressure usually fell to the abscissa line and no further waves were recorded upon the drum. It was only after the pressure had reached the abscissa line, after all pulse waves had ceased, and no heart sound, however feeble, could be auscultated, that we recorded the moment of death. The time was then extended to five, ten, fifteen, twenty, and thirty minutes in adult dogs, and in puppies up to an hour.

The limitations of the method soon appeared. Among them were the following: (a) ante-mortem clotting, (b) over-distension of the heart, (c) later failure of the heart, circulation, and respiration, (d) the apparently imperfect recovery of the brain.

Ante-mortem Clotting.—When a considerable time had elapsed, say ten minutes or more after death, and particularly if there had been some delay in resuscitation of the heart, thereby inducing vigorous and protracted massage, clotting occurred more frequently. Direct cardiac massage was then made, which seemed further to facilitate clotting. In other cases indirect massage was made with extreme vigor, showing like results. Finally, an animal was etherized to the point of respiratory failure, then sustained with a very low blood pressure by means of artificial respiration combined with vigorous cardiac massage, for a period of about seven minutes, after which the heart was opened before it had ceased beating and small clots were found. No infusion in this case had been given and no other operation was performed. This seemed to confirm our previous conclusion that either vigorous or prolonged massage of the heart predisposed to ante-mortem clotting and that direct massage of the heart favored clotting more than indirect massage by rhythmic pressure upon the intact thorax over the heart.

It was found that animals could be resuscitated after several compressions of the chest by waiting a little longer for the rise in the pressure from the adrenalin infusion alone. It was obvious that in our previous experiments we gave unnecessary massage as to force, frequency, and duration. This is the more reasonable since the object of the massage is not that it will materially aid the heart in *inaugurating* its rhythmic contractions, but that it will distribute the fluid through the circulation which has been injected by gravity alone. Pressing upon the thorax itself, would effect a certain amount of circulation, if no heart existed and a system of vessels, one having valves and the other not, replaced it, and in the dead animal pressure upon the thorax alone is capable of producing an artificial circulation. This is by no means accomplished by its action upon the heart solely, but by its action upon all the large vessels—arteries, veins, and capillaries together.

We also observed what on *a priori* grounds we supposed to be true, namely, that a tendency to clotting was increased in a direct ratio with the lapse of time. When clotting occurred resuscitation was practically always impossible. The heart would beat for a short time, but the beat would soon fade away.

Over-distension of the Heart.—In the unsuccessful cases, particularly those in which a considerable amount of infusion was given, the heart at autopsy was found over-distended. This over-distension was due to two factors; the first was the inevitable accumulation of blood in the heart during its gradual failure either in asphyxia or following chloroform and ether; second, the infused fluid passed through the coronary arteries, through the coronary vein into the right side of the heart. The left heart was not generally so distended as the right heart. It is obvious that if for any reason resuscitation is not promptly made the accumulation of fluid in the right heart must not only be considerable but must occur under pressure; since the valves prevent the escape of the fluid toward the periphery of the veins the accumulation must be largely in the heart itself, and when this condition is reached a peculiar vicious circle has been established. The greater the efforts at resuscitation by increasing the infusion the greater the distension of the paralyzed ventricle and the more certain is the failure of the attempt. In some instances after the chest was opened and the heart on inspection was found distended, rhythmic contractions of the heart began; on opening the pericardium in one instance a splendid resuscitation (Fig. 6.) was made.

Later Failure of the Heart, Circulation, and Respiration.—In a number of instances after a temporary resuscitation the circulation and the respiration failed, after which a second attempt at resuscitation was useless. In these cases the failure was generally gradual and occurred after the lapse of a varying period of time, ranging from three and a half to twenty hours. In these cases for the most part ten minutes or more had elapsed before resuscitation was attempted. A few animals in which resuscitation was attempted in less than ten minutes also showed later failure. We are not prepared to state the exact cause of this later failure.

The Apparently Imperfect Recovery of the Brain Proper.—In resuscitations after ten minutes, particularly those after from fifteen to twenty minutes, it was noted that while the circulation and the respiration were satisfactory the animal did not regain consciousness; the reason for this we are not at present prepared to state, but it will be further investigated.

We also investigated the influence of prolonged chloroform anesthesia prior to death. Animals were kept under chloroform anesthesia for an hour and then killed by an over-dose. They were resuscitated perhaps a little less readily than the animals killed immediately by an over-dose, though their resuscitation was, up to ten minutes, satisfactory.

Hirudin.—After encountering the difficulty with clotting in the delayed cases, we tested the value of hirudin in the prevention of clotting. In the cases in which hirudin was given prior to death no clotting occurred in a single instance in the heart or blood-vessels. In these cases, which were limited to puppies not over three months old, we are, however, inclined to believe that œdema of the lungs was distinctly more marked. The blood seemed to lose its viscosity and the œdematous fluid accumulated rapidly in the bronchial tubes, and finally flowed out of the trachea, presenting a reddish tinge. In the successful cases this always occurred before the inauguration of the heart-beat. There was in addition free blood-tinged fluid in the thorax. While hirudin, in the case of puppies at least, entirely obviates the clotting factor it introduces an equally fatal obstacle, *i. e.*, waterlogging of the thorax, which we were not able to prevent by reducing the infusion pressure to a minimum consistent with its efficacy.

Puppies.—The experiments on puppies showed at once that resuscitation was more readily done, and successful after a longer period after death, than in the adult dog. In three instance thirty-five minutes after death a fairly good circulation was obtained (Fig. 8).

Solution Employed for Infusion.—The observations in this series as well as in other researches within the past year have led us to conclude that Ringer's solution yields more favorable results than saline solution. The most satisfactory results were obtained with the infusion bottle at a height of five or six feet.

Conclusions.—Based on the data supplied by these researches and those of preceding researches on similar lines we arrive at the following conclusions:

(1) Animals after death from chloroform, ether, or asphyxia up to five minutes were uniformly and readily resuscitated,

provided that the full techinque which has been described was applied; up to ten minutes there was an occasional failure; beyond ten minutes consciousness was rarely restored, and the proportion of successes in the resuscitation of the circulation and the respiration diminished with the lapse of time; after twenty-three minutes in adult dogs and thirty-five minutes in puppies complete return of the circulation was not accomplished.

(2) After death from chloroform and ether animals were more readily resuscitated than after death from asphyxia.

(3) Resuscitation, if successful, occurred within one minute after the administration of adrenalin in the majority of instances; it rarely occurred after an interval greater than three minutes.

(4) The greatest difficulty to be overcome was clotting. The probability of clotting increased in direct ratio with the lapse of time after death. Cardiac trauma predisposed to clotting.

(5) The younger the animal, up to certain limits, the more readily it was resuscitated.

(6) Any artery may be used for the infusion, though the advantage is probably slightly in favor of the carotid. The infusion should be directed toward the heart.

(7) The probable success of resuscitation is greater in inverse relation to the lapse of time after death; a rapid rise in the arterial pressure is attained by arterial infusion with a therapeutic dose of adrenalin, together with good artificial respiration and the avoidance of unnecessary cardiac trauma by massage. All artificial aids should cease as soon as the functions are competent.

ILLUSTRATIVE PROTOCOLS.

EXPERIMENT IV. *The effect of time and of massage on the formation of clots* Mongrel mastiff, 20 K. Chloroform administered until death.

10.09—Respiration stopped.

10.14—Pulse was not palpable at carotid.

10.15—Heart sounds ceased. The opened carotid bled for some time with a non-pulsating drop flow which stopped when the head was raised. A tracheal cannula was rapidly adjusted, and with a manometer cannula in the left carotid a small cannula in the right carotid was connected with the saline infusion bottle at a height of seven feet. A pin-hole cannula in the left femoral vein was connected to an infusion bottle containing 1–100000 solution of adrenalin chloride at a height of three feet.

10.47 (32 minutes)—Resuscitation attempted. Cardiac massage was vigorous. Two cubic centimeters of the solution of adrenalin chloride were injected into the infusion tubing. No results came from the first dose of adrenalin within two minutes. With a second dose there was a perceptible manometer pulse and measures were temporarily stopped, the blood pressure being 40 mm., but the level quickly declined to the abscissa. Further efforts, namely massage and a mass dose of adrenalin with a continuous 1–100000 infusion into the femoral vein, failed to improve the heart-beat and to raise the blood pressure. After some time, when no pulse could be felt, the carotid infusion was again started and a second time beats were evoked, but other measures failed to keep up the heart's activity. In the latter part of the experiment the dog's feet were lowered.

At autopsy the heart was full of bloody fluid, the pericardium was tense and the heart dilated. Clots were found in the heart.

Experiment xxviii. *Resuscitation six minutes after death.* (Fig. 1.) Ether anesthesia. This experiment was performed with moderate aseptic precautions.

10.59—Control blood pressure 156 mm.

11.00—Began to force ether.

11.04—Respiration stopped, after which cardiac failure gradually ensued.

11.06—Heart sounds ceased and pulse not palpable.

11.12—Resuscitation was begun (6 minutes). Saline infusion plus 2 c.c. of adrenalin chloride (1–1000) was administered through the axillary artery together with artificial respiration and gentle heart massage. About twenty respirations were given. The heart began to beat in about one and a half minutes. The blood pressure rose sharply to 240 mm., which level was sustained for several minutes. It gradually fell to 80 mm., at 11.24.

11.18—Spontaneous respiration began.

11.20—Ether was required and given. The respiration was at first very irregular and spasmodic, gradually becoming quiet and regular.

11.29—Blood pressure 130 mm.

11.40—Blood pressure 160 mm.

11.50—Blood pressure 160 mm. The trachea was sewed up, the wounds in the neck and axilla were closed with large gauze drainage and were bandaged. The dog was removed from the table and allowed to recover. Late in the afternoon the dog had considerable respiratory difficulty, apparently due to obstruction in the trachea. The animal was etherized, a blood clot was removed from the trachea, a cannula inserted, and the neck bandaged.

The next morning his condition was good and he was walking about, but as considerable pus was coming from the tracheal cannula it was decided to kill him. He was etherized and the carotid artery was again connected with the manometer.

10.30—Blood pressure 106 mm.

11.00—Blood pressure 112 mm.: the difference being due to the depth of anesthesia. The dog was then killed.

Beyond the infection about the trachea, there were no macroscopic lesions found at autopsy.

Experiment xix. *Resuscitation five minutes after apparent death.* (Fig. 2.) Mongrel in rather poor condition; weight 7.3 K. Anesthetized with ether.

10.35—Control blood pressure 140 mm.

10.42—Trachea clamped. Several control determinations of blood pressure showing stages of asphyxia were made.

10.44—Last respiration occurred.

10.47—Heart sounds had ceased, and pulse was not palpable.

10.54½—Resuscitation started: Infusion of saline through axillary artery, the infusion bottle being placed at a height of five feet, plus two c.c. solution of adrenalin; artificial respiration was begun at 10.55 without any heart massage. The heart began to beat in about one minute, the blood pressure rising quickly to 206 mm. from which it gradually declined to 130 mm. at 11.10.

11.07—Spontaneous respirations occurred. Artificial respiration was stopped.

11.18—Ether required.

11.50—Control blood pressure 128 mm.

12.05—Control blood pressure 122 mm.

11.15—Control blood pressure 122 mm. Ten mg. of morphine per kilo was administered. Ether was discontinued.

2.05—Control, blood pressure 108 mm.

2.21—Control. The animal was killed as soon as recovery was apparent.

4.41—Control taken. Five hours and forty minutes after resuscitation the dog's condition was excellent, but on account of the septic condition of the operative wounds he was killed.

EXPERIMENT XLVII. *Temporary Resuscitation.* (Fig. 3.) Mongrel weighing about 10 K.

10.20—Anesthesia with ether started.

10.59—Control blood pressure 110 mm.

11.06—Trachea clamped.

11.09¾—Control showing a stage of asphyxia.

11.11¾—Control showing a stage of asphyxia.

11.12—Heart sounds ceased and pulse was not palpable.

11.22—Started resuscitation (10 minutes). Infusion of Ringer's solution, plus 2 c.c. of adrenalin (1—1000) was given through axillary artery, artificial respiration and firm but gentle heart massage were started simultaneously. The heart beat after two minutes, the blood pressure rising to 220 mm. with the typical adrenalin effect. This level was maintained for over three minutes and the decline was gradual.

11.31—Control blood pressure 180 mm.

11.35—Control blood pressure 80 mm. Pulse wave much smaller. Burning of paw evoked no reaction. There were no corneal reflexes.

11.40—Spontaneous respiration occurred. Control.

11.45—Control blood pressure 50 mm. Pulse wave improved.

11.55½—Control blood pressure 60 mm. Artificial respiration stopped. No corneal reflexes, feeble knee jerk in right hind leg.

12.00½—Control. Sharp reaction to paw burning, followed by a secondary reaction with the higher level maintained. Knee jerk appears in left hind leg.

12.07—Control blood pressure 80 mm. Dilating and burning the anus evokes a vasomotor rise, but no respiratory reflex. Corneal reflex appears in right eye. Pupils were extremely dilated after resuscitation, but now are narrowed to some extent. They do not react to light.

12.15—Control blood pressure 50 mm. Pulse wave weaker. Corneal reflex appears in left eye. Respirations have assumed a normal rhythm.

1.06½—Control blood pressure 50 mm. Corneal reflexes improved. Incompetence of sphincters. The animal is entirely anesthetized to pain and completely unconscious. Rigidity of the hind legs appears. Respirations are becoming more labored and quicker.

2.00—Pupils slowly dilating. Left front leg now resists passive motion slightly. Right front leg is entirely relaxed.

2.45—Front legs are also stiffened. Vasomotor reflex is disappearing. Knee jerks cannot be obtained.

3.00—Control blood pressure 50 mm.

3.15—Rapid cardiac failure.

The only finding at autopsy was œdema of the posterior parts of the lungs which explained the change in the character of the respirations.

Experiment xxxviii. *Failure to resuscitate the higher centres of the brain.* (Fig. 4.) Pug dog weighing 15.9 K.

10.45—Anesthetized with ether, changing at once to chloroform.

11.25—Control blood pressure 110 mm.

11.37 (52 minutes)—Chloroform forced.

11.37¾—Control.

11.38¼—Respiration stopped; cardiac failure followed quickly.

11.39½—No heart sounds.

11.40½—Control. Heart-beats recurred.

11.42—Final cardiac failure.

11.52 (10 minutes)—Started resuscitation. Infusion of Ringer's fluid through axillary artery, plus artificial respiration, was continued for one and a half minutes, and then 1 c.c. of adrenalin was administered. After waiting one and a half minutes, firm, slow massage of the chest was instituted. After a half minute the heart began to beat and the blood pressure rose to 250 mm. from which apex it quickly declined to 80 mm. in about three minutes, the pulse wave growing progressively larger. Drum stopped.

12.07—Control blood pressure 72 mm. This lowering of the pressure occurred synchronously with lowering the dog's feet.

12.11—First spontaneous respiration.

12.13—Control, showing respiratory curve of the blood pressure.

12.17—Control; clot.

12.21—Control blood pressure 90 mm. Artificial respiration stopped.

12.30—Control blood pressure 120 mm. Tracheal cannula out of position.

1.37—Control blood pressure 70 mm.

1.38—Control. Distinct reaction to burning of paw. Corneal reflexes are barely present. No anesthetic required.

2.00—Control blood pressure 84 mm. The dog was in such excellent shape that it was decided to allow him to recover. After the wounds were closed leaving the tracheal cannula in, he was removed from the table.

5.00 (5 hours)—Animal in good shape but unconscious. No ether had been required. Found dead the next morning.

All the organs and tissues presented at autopsy evidence of infection with B. aerogenes capsulatus. There were no clots in the heart and no macroscopical lesions of the viscera other than the post mortem infection noted.

Experiment xlii. *Resuscitation of smaller part of brain after lapse of more time.* (Fig. 5.) Mongrel, 6.9 K., emaciated but healthy looking

10.15—Anesthetized with chloroform.

11.13—Chloroform forced (anesthesia during one hour).

11.17¾—Heart stopped before respiration according to manometer tracing.

11.19—Heart-beats recurred for about ten seconds.

11.20—Heart-beats recurred a second time, about twelve in all being recorded.

11.20¼—Heart sounds ceased and the pulse was not palpable.

11.40¼ (20 minutes)—Resuscitation started. Infusion of Ringer's fluid through axillary artery, plus 2 c.c. of solution of adrenalin chloride (1—1000), and artificial respiration were started simultaneously. Gentle pressure at intervals on the chest with the feet lowered was also used. After several minutes the axillary cannula pulled out and was refixed in the right carotid.

11.43 (23 minutes)—Resuscitation was again attempted, artificial respiration having been kept up continuously. In about a minute the heart was noticed to be beating. The blood pressure curve rose rather slowly to a height of 110 mm. with a very irregular pulse wave.

11.48—Respiration recurred.

11.49—Control: blood pressure level has fallen to 50 mm.

12.07—Control blood pressure 36 mm. Burning of paw evokes no reaction.

12.20—Blood pressure 50 mm. Pulse wave much improved. Faint corneal reflex in right eye.

2.00—Control blood pressure 54 mm. Respirations have become more normal in type, but the heart rate is distinctly lowered. Burning of paw evokes a very slight rising of blood pressure only. Knee jerks are present in both hind legs. Corneal reflex is present in the right eye, though feebler than normal; it is just perceptible and delayed in the left. Dog appears insensible to touch sensation, but burning anus causes spontaneous movements of the legs. The pupils do not react to light. The right pupil is more dilated than the left.

4.00—Control, showing rise of pressure due to accidental asphyxia.

4.30—Control blood pressure fallen to 28 mm.

Ante-mortem examination was performed. No clot appeared in the heart and the viscera were apparently normal.

EXPERIMENT XLVIII. *Partial resuscitation of a puppy thirty minutes after apparent death.* (Fig. 7.) Skye terrier puppy, three months old, weight 2 K. anesthetized with ether. A full dose of hirudin—10 c.c. of a .4 of 1% solution —was given to obviate clotting.

2.55—Control blood pressure 104 mm. Chloroform exchanged for ether and forced.

3.03½—Respiration stopped. Control.

3.06—Heart sounds, then pulse, not perceptible.

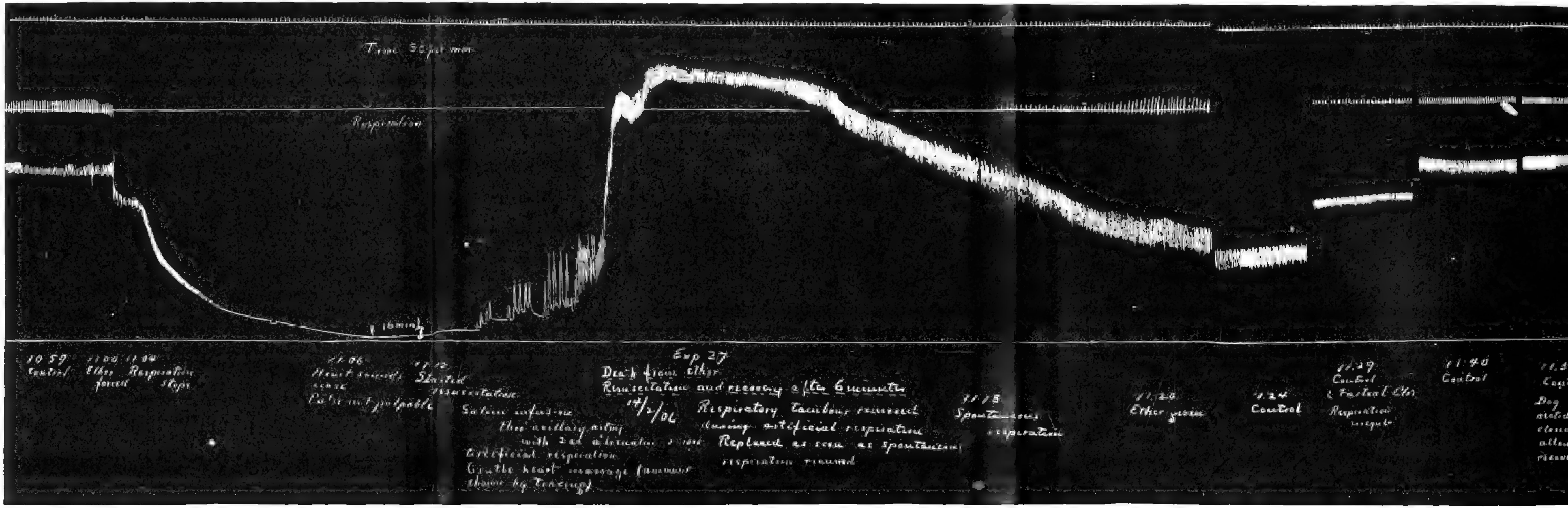
3.36 (30 minutes)—Began resuscitation. Infusion of Ringer's solution from the height of four feet, plus 2.5 c.c. of 1—1000 adrenalin through carotid artery, with artificial respiration and gentle heart massage, were started simultaneously. Heart began to beat in about two minutes. Infusion was stopped as soon as the blood pressure began to rise decidedly. In about three minutes the blood pressure reached a height of 94 mm., with a regular and rhythmic heartbeat of good strength.

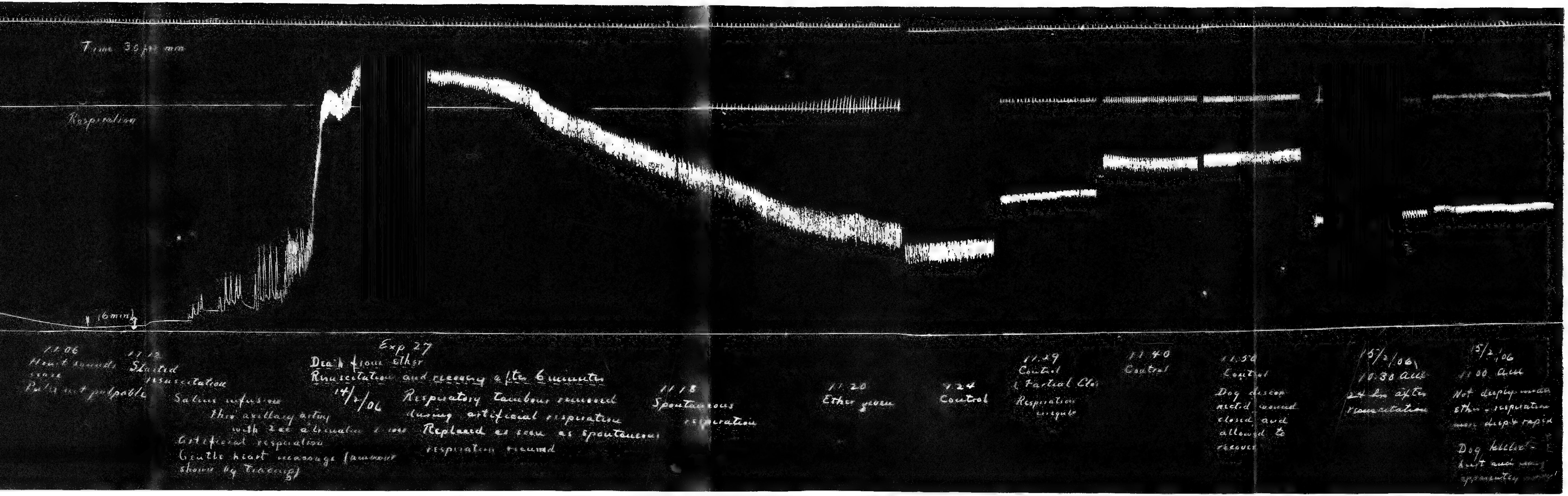
3.41—Drum stopped.

3.50—Control blood pressure 102 mm.

Summary of Experiments

Experiment	Mode of death	Duration of suspended animation (In minutes)		Infusion	Massage	Heart beat: Circulation not maintained	Complete return of circulation.	Length of survival	Respiratory recovery	Vaso-motor recovery	Approximate time of return of heart beat.	Total duration of suspended respiration	Clot	Cardiac dilatation	REMARKS
		Heart	Resp.												
1	Chloroform	2	—	Saline.	Indirect	o	+	½ hr.	+	—	¼ min.	—	—	—	
2	Asphyxia.	5	—	"	Direct.	+	—	7 min.	o	o	6 min.	—	?	—	Window in chest.
3	"	10½	11	"	Vigorous; indirect	+		Short	o	o	1 min.	—	?	+	Infusion very rapid.
4	Chloroform	5½	—	"	" "		+	1¾ h. (killed)	o	+	at once	—	?	—	Gréhant anesthesia.
5	"	11	21	"	" "		+	10 min.	+	o	2 min.	—	?	—	Death due to accidental hemorrhage.
6	"	6	25	"	" "	+		12 min.	o	o	2 min.	—	?	+	Rapid infusion.
7	"	21	36	"	" "	+		12 min.	o	?	1 min.	—	?	—	Repeated doses of adrenalin till ineffectual.
8	"	30	36	"	" "	+		Short	o	o	?	—	?	+	Infusion kept up too long.
9	"	32	38	"	" "	+		Short	o	o	Delayed	—	?	—	Effort not uniform nor continuous.
10	Asphyxia.	30	33	"	" "	o		o	o	o	—	—	?	—	Absolute failure.
11	"	15	19	"	" "	o		o	o	o	—	—	?	—	" "
12	"	15	—	"	" "	o		o	o	o	—	—	?	—	"
13	"	11½	16¼	"	" "	o		o	o	o	—	—	?	—	Delay after starting; auricular appendages beating.
14	Chloroform	6	—	"	Very vigorous		+	3 days (killed)	+	+	1 min.	—	+	—	Clots at atuopsy in heart.
15	"	17	21	"	Vigorous.	+(?)		?	o	o	—	—	+	—	Feeble rythmic beat of right heart at autopsy.
16	Asphyxia.	11	13	"	"	+		Short	o	o	—	—	+	—	
17	"	10½	11½	"	Gentle then direct	+		15 min.	o	o	—	—	+	—	Heart started by direct manipulation.
18	Ether	10	17	"	Vigorous.	+		Short	o	o	Delayed	—	+	—	Massage after failure of first efforts.
19	Asphyxia	7½	10½	"	o		+	6 hrs. (killed)	+	+	1 min.	23 min.	o	o	
20	Ether	7	7½	"	o	o		o	o	o	—	—	+	—	No massage for 8 min.; auricular appendages beat.
21				o	Vigorous								o		Vigorous massage of beating heart.
22				o	"								+		Vigorous massage of dying heart.
23				o	"								o		Vigorous massage with vagus inhibition.
24	Ether	5	10½	Saline	o	o			o	o	—	—	+	+	Vigorous massage after 2½ min.
25	Chloroform	9	13	"	Gentle	o			o	o	—	—	+	+	Dilatation factor in clotting?
26	"	7	12½	"	o	o			o	o	—	—	+	+	Clotting without massage.
27	Ether	10	—	"	o		+	(killed)	o	o	1 min.	—	o	o	Kitten. Accidental air embolism.
28	"	6	8	"	Gentle		+	24 hrs. (killed)	+	+	1½ min.	14 min.	o	o	Would have survived.
29	"	15	17	"	Late	o			o	o	—	—	+	—	Puppy; mass clots.
30	"	15	24	"	Gentle		+	3½ hrs.	+	Failed	2 + min.	40 min.	o	o	Puppy; hirudin; died.
31	Chloroform	7	13	"	"		+	20 hrs.	+	+	3 min.	22½ min.	o	o	Found dead.
32	"	6½	—	"	"	o	—	—	o	o	—	—	o	o	Chloroform 1 hour; no artificial respiration.
33	"	5	5+	"	After 1 min.	o	—	—	o	o	—	—		+	Rigid chest; old dog.
34	"	5	5½	"	After 1 min.	o	—	—	o	o	—	—	+	+	Chloroform 1¼ hours; arythmic beat of auricles
35	"	6½	16½	"	Vigorous	+		Failed at once	o	o	—	—	+	?	Left in hands of janitor.
36	"	5	10	"	Firm	o		—	o	o	—	—	+	+	Clotting in infusion cannula after starting.
37	"	5	8	"	After 2 min.		+	20 hrs.	+	+	1 min.	13 min.	o	o	Chloroform ½ hour; delay of 3½ min. after starting.
38	"	7½	9½	Ringer	o	+		Failed at once	o	o	1 min.	—	o	o	Chloroform 1 hour; possible over-stimulation of moribund heart.
39	"	10	13¾	"	Gentle		+	15 hrs. died	+	+	½ min.	32¾ min.	o	o	Chloroform 50 min.
40	"	at once	—	Saline	Vigorous		+	15 min. (killed)	+	—	3 min.	—	o	o	Ether 1½ hours; dilatation overcome by massage and position.
41	"	12¾	13	Ringer	Gentle		+	15 hrs. died	+	+	Under 3 m.	23¾ min.	o	o	Chloroform 1 hour; recovered enough to walk.
42	"	20	21	"	"		+	Short (killed)	—	—	3 + min.	—	o	+	Chloroform 50 minutes; freeing heart started beating.
43	"	20 (23)	32½	"	At intervals		+	4½ hrs. (died)	+	+	1 min.	40 min.	o	o	Delay of 3 minutes just at start.
44	"	30	33½	"	Gentle	o		—	o	o	—	—	o	o	Slow infusion.
45	"	30	32½	"	Later vigorous	o		—	o	o	—	—	+	+	Vigorous massage later.
46	Asphyxia	18¾	21¾	"	"	o	—	—	o	o	—	—	+	+	
47	Ether	25	—	"	"	o		—	o	o	—	—	+	+	Massage later after first failure.
48	Asphyxia	10	—	"	Gentle		+	3¾ hrs. (died)	+	+	2 min.	28 min.	o	o	
49	Chloroform	30	32½	"	"		+	2½ hrs. (died)	+	+	2 min.	53½ min.	o	o	Puppy; hirudin; respiration and blood pressure failed.
50	"	60	61	"	"	o	—	—	o	o	—	—	o	+	Puppy; hirudin; oedema of lungs.
51	"	45	46	"	"	o		—	o	o	—	—	o	+	" " "
52	"	35	36	"	"	+	+	Short	o	o	3 min.	—	o	+	" " "
53	"	40	40½	"	"	o		—	o	o	—	—	o	+	" " "
54	"	35	36½	"	"	o		—	o	o	—	—	o	+	" " "
55	"	35	36½	"	"		+	Short	o	o	3 + min.	—	o	+	" " "
56	"	30½	32½	"	o	o		—	o	o	—	—	o	+	" " "
57	"	35	36	"	Gentle		+	Short	o	o	5 min.	—	o	+	" no hirudin.
58	"	7	—	"	"		+	—	+	—	2½ min.	—	o	o	For demonstration.
59	"	10	—	"	"		+	—	+	—	2 min.	—	o	o	" "
60	"	8	—	"	"		+	—	+	—	—	—	o	o	" "


Time 30 per min
Respiration
16 min
10.59
Control
11.00 11.04
Ether forced
Respiration stops
11.06
Heart sounds cease
Pulse not palpable
11.12
Started resuscitation
Saline infusion
thro' axillary artery
with 2cc adrenalin 1:1000
Artificial respiration
Gentle heart massage (movements shown by tracing)
Exp 27
Death from ether
Resuscitation and recovery after 6 minutes
14/2/06
Respiratory tambour removed
during artificial respiration
Replaced as soon as spontaneous
respiration resumed
11.18
Spontaneous
respiration
11.20
Ether given
11.24
Control
11.29
Control
& Partial Ether
Respiration
irregular
11.40
Control


Time 30 per min
Respiration
16 min
11.06
Heart sounds cease
Pulse not palpable
11.12
Started resuscitation
Saline infusion thro axillary artery with 2cc adrenalin [illegible]
Artificial respiration
Gentle heart massage (amount shown by tracing)
Exp 27
Death from ether
Resuscitation and recovery after 6 minutes
14/2/06
Respiratory tambour removed during artificial respiration
Replaced as soon as spontaneous respiration resumed
11.18
Spontaneous respiration
11.20
Ether given
11.24
Control
11.29
Control
& Partial Clo
Respiration irregular
11.40
Control
11.50
Control
Dog disconnected wound closed and allowed to recover
15/2/06
10.30 am
24 hrs after resuscitation
15/2/06
11.00 am
Not deeply under ether - respiration more deep & rapid
Dog killed - heart and lungs apparently normal

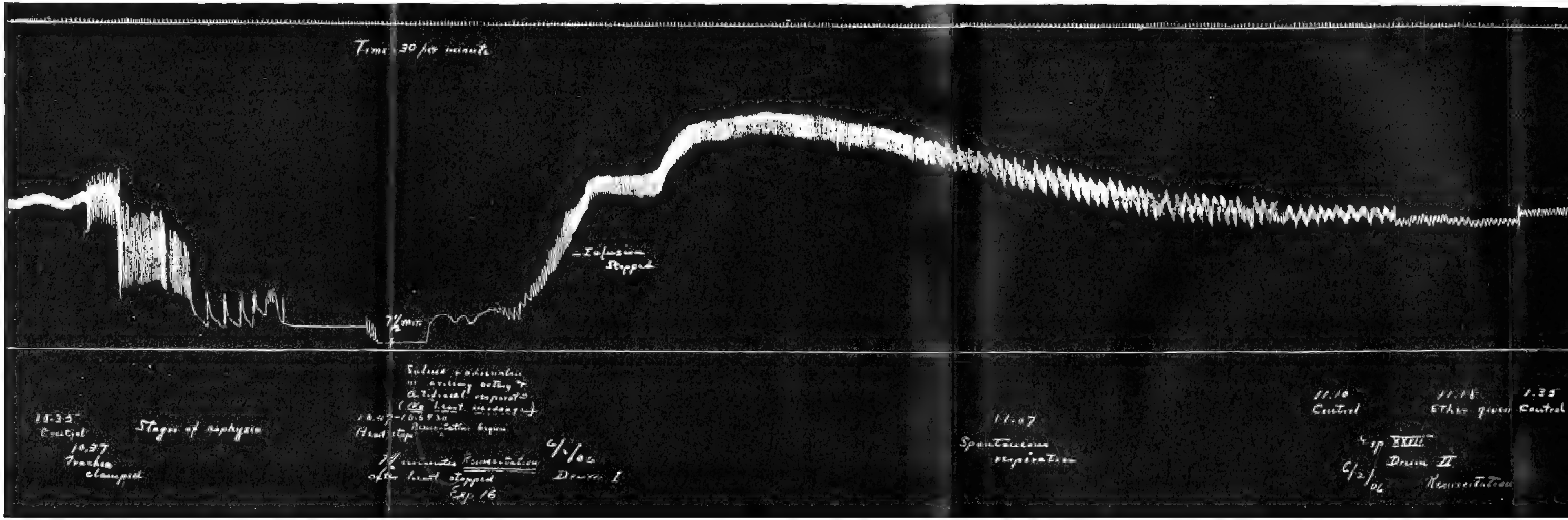
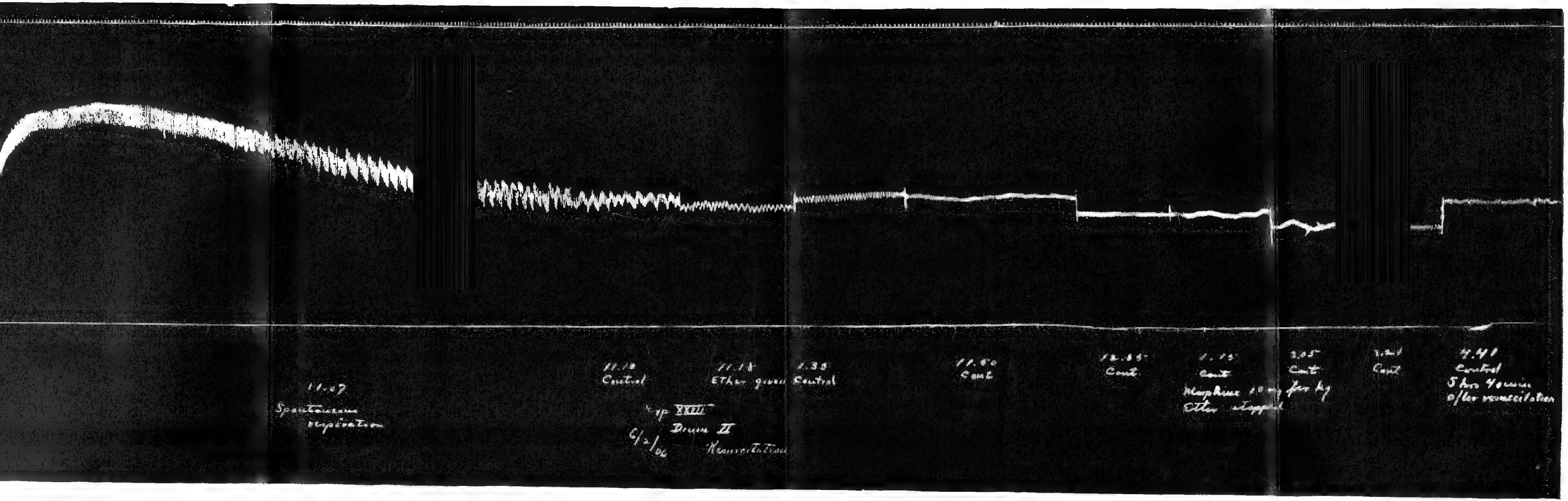

Time 30 per minute
7½ min
Infusion stopped
10.35
Control
10.37
Trachea clamped
Stages of asphyxia
10.47-10.59 30
Heart stops
Resuscitation begun
Saline ... in axillary artery & artificial respiration
(... heart massage)
7½ minutes Resuscitation after heart stopped
Exp. 16
6/1/06
Drum I
11.07
Spontaneous respiration
11.10
Control
11.18
Ether given
1.35
Control
Exp XXIII
Drum II
6/2/06
Resuscitation

PLATE XLIII.



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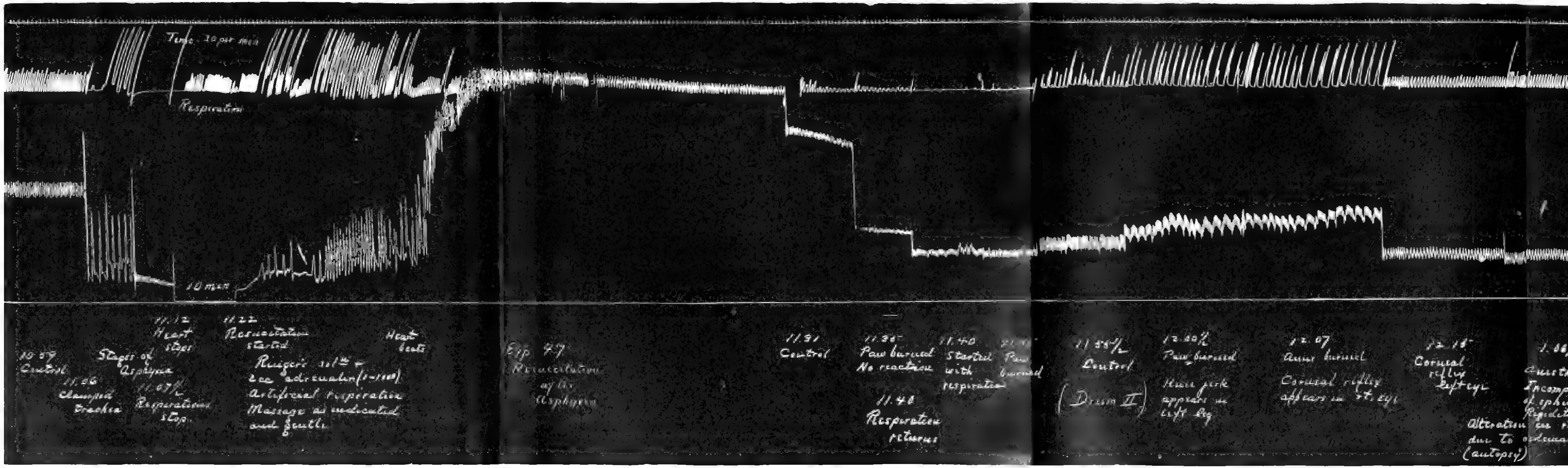
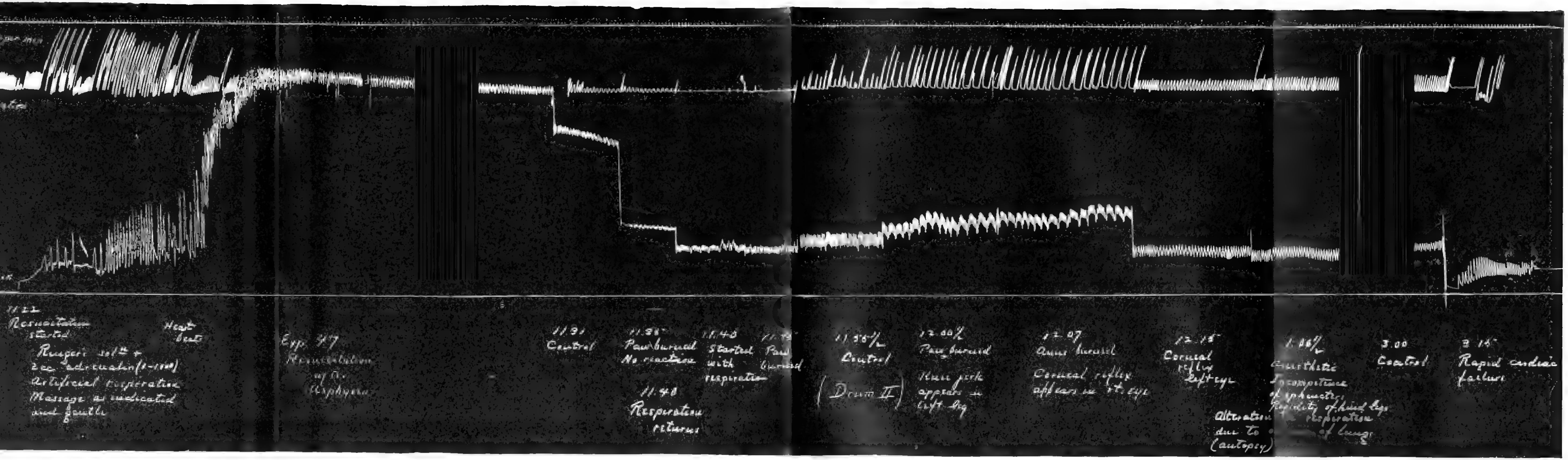
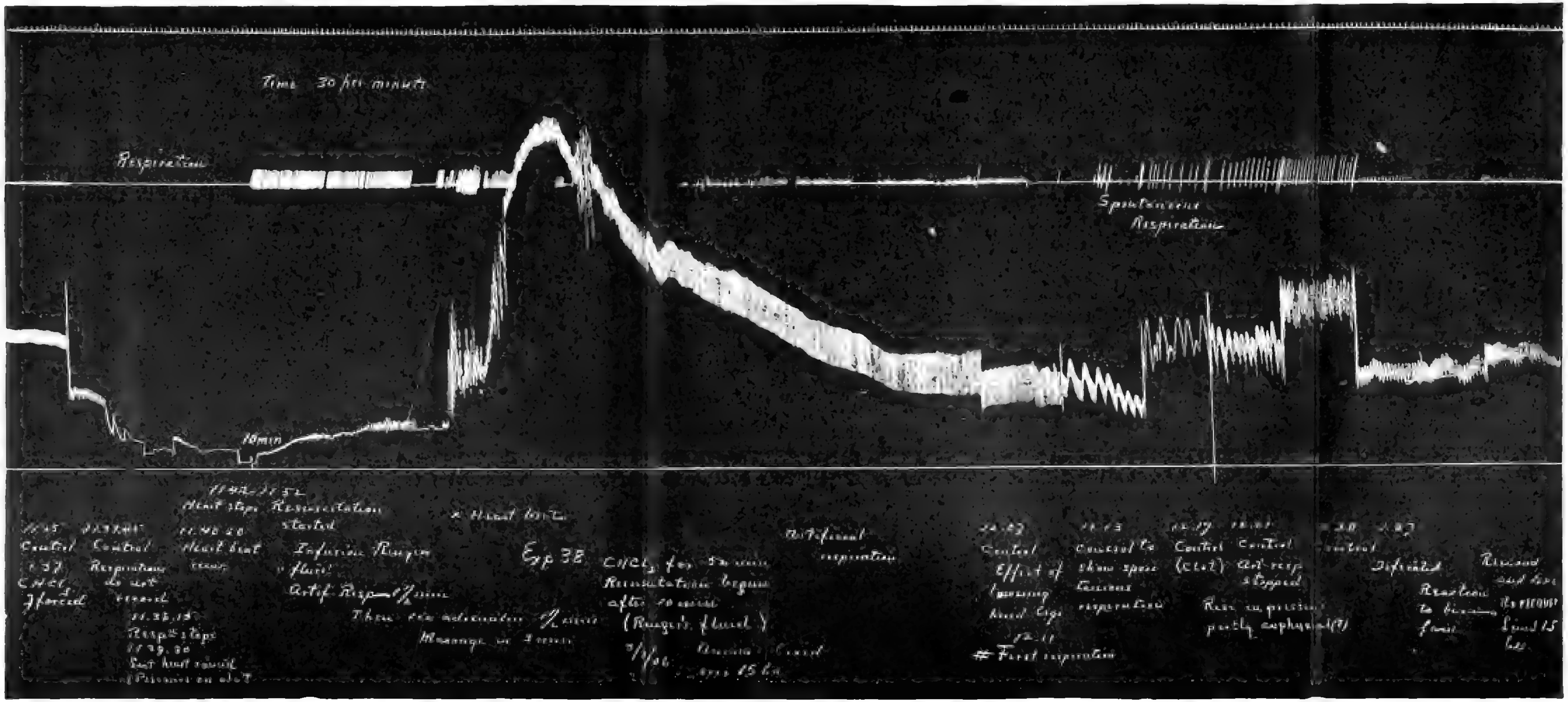
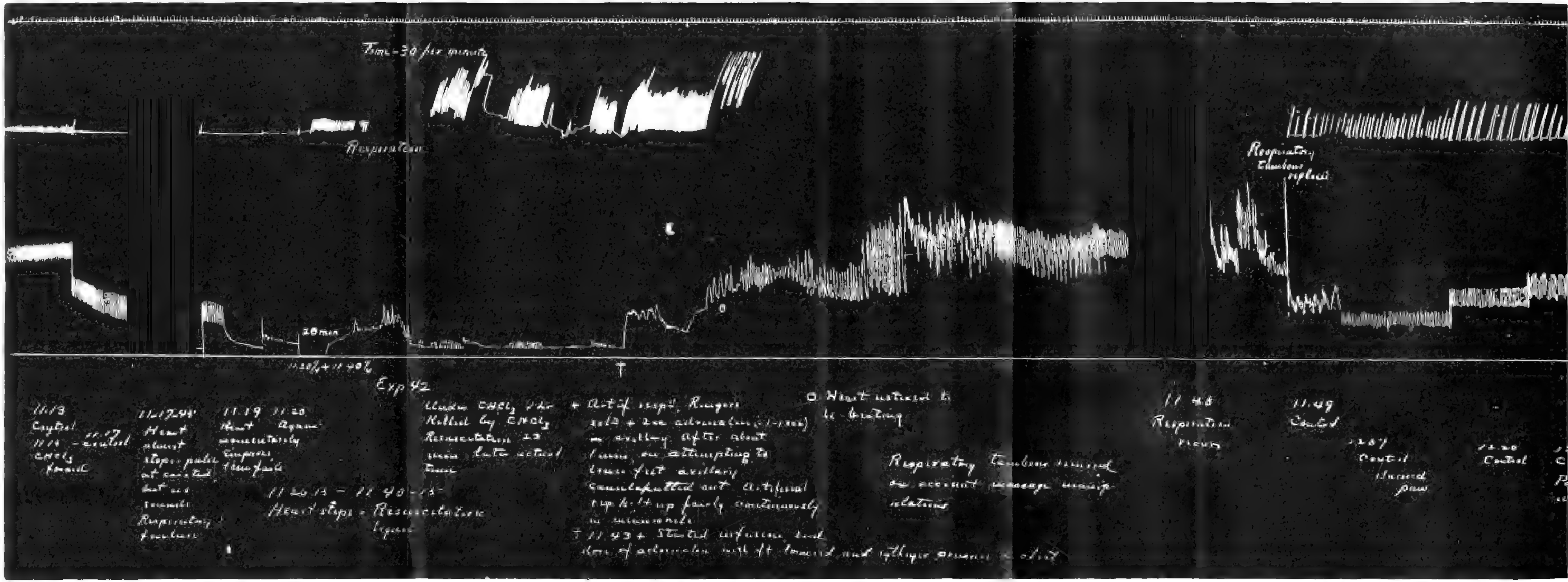
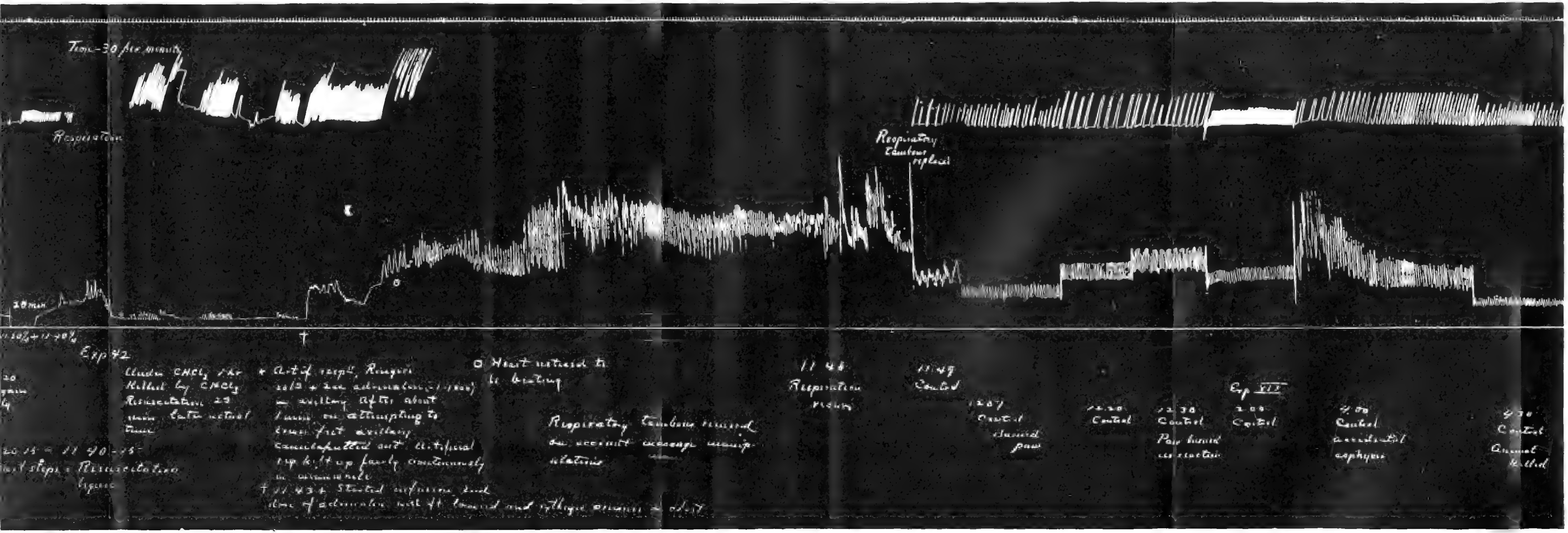

Time. 30 per min
Respiration
10 min
10.59 Control
11.06 Clamped trachea
Stages of Asphyxia
11.07½ Respirations stop.
11.12 Heart stops
11.22 Resuscitation started
Ringer's sol.ⁿ + 2cc adrenalin (1–1000)
Artificial respiration
Massage as indicated and gentle
Heart beats
Exp. 47
Resuscitation after Asphyxia
11.31 Control
11.35 Paw burned
No reaction
11.40 Started with respiration
Paw burned
11.48 Respiration returns
11.55½ Control
(Drum II)
12.00½ Paw burned
Hind jerk appears in left leg
12.07 Anus burned
Corneal reflex appears in rt. eye
12.15 Corneal reflex Left eye
Alteration
due to
(autopsy)

PLATE XLIV.


11.22
Resuscitation started
Heart beats
Ringer's sol^n + 2cc. adrenalin (1-1000)
Artificial respiration
Massage as indicated and gentle
Exp. 47
Resuscitation after Asphyxia
11.31
Control
11.35
Paw burned
No reaction
11.40
Started with respiration
11.45
Paw burned
11.48
Respiration returns
11.55½
Control
(Drum II)
12.00½
Paw burned
Knee jerk appears in left leg
12.07
Anus burned
Corneal reflex appears in rt. eye
12.15
Corneal reflex left eye
Alteration due to
(autopsy)
1.00½
Anesthetic
Incompetence of sphincters
Rigidity of hind legs
respiration
of lungs
3.00
Control
3.15
Rapid cardiac failure


Time 30 per minute
Respiration
Spontaneous Respiration
10 min
11.45 Control
1.37 CHCl3 forced
Control Respirations do not record
11.36.15 Respns stops
11.39.30
11.42-11.52 Heart stops Resuscitation started
11.48.50 Heart beat
Infusion Ringer's fluid
Artif. Resp.
x Heart beat
Massage in 3 min
Exp 38
CHCl3 for ... min
Resuscitation begun after 10 min
(Ringer's fluid)
Artificial respiration
Control
Effect of lowering head
12.11
# First inspiration
Control to show spontaneous respiration
Control (CO2)
Control Art. resp. stopped
Control
Rise in pressure partly asphyxial (?)
Reaction to ... fumes
Removed and dog recovered
Lived 15 hrs


Time–30 per minute
Respiration
Respiratory tambour replaced
20 min
11.20½ + 11.40½
Exp 42
11.13 Carotid 11.14 – CHCl3 period
11.17 – carotid
11.17.44 Heart almost stops: pulse at carotid but no tracing. Respiratory failure
11.19 11.20 Heart again momentarily improves then fails
11.20.13 – 11.40.15 Heart stops – Resuscitation begun
Under CHCl3 1 hr Killed by CHCl3 Resuscitation 20 min. later actual time
+ Artif. resp., Ringer's 200 + 2cc adrenalin (1-1000) in axillary. After about 1 min, on attempting to turn out axillary cannula pulled out. Artificial resp. kept up fairly continuously in intervals
† 11.43 + Started infusion and dose of adrenalin with ft. lowered and rythmic pressure on chest
O Heart noticed to be beating
Respiratory tambour removed on account massage manipulations
11.48 Respiration begun
11.49 Carotid
12.07 Carotid Burned paw
12.20 Control


Time—30 per minute
Respiration
20 min
11 10% + 11 20%
Exp 42
20
gain
4
Under CHCl3 the
Killed by CHCl3
Resuscitation 29
min. later actual
time
20.15 = 11 40-15
t steps = Resuscitation
figures
* Artif. resp., Ringer's
sol. + 2cc adrenalin (1:1000)
in axillary. After about
1 min. on attempting to
cannulate 2nd axillary
cannula jutted out. Artificial
resp. kept up fairly continuously
in interval
† 11.43+ Started infusion and
dose of adrenalin until ht. lowered and rhythm [illegible]
○ Heart noticed to
be beating
Respiratory tambour raised
on account massage manip-
ulation
11 48
Respiration
return
Respiratory
tambour
replaced
11.49
Control
12.07
Control
clamped
paw
12.20
Control
12.30
Control
Paw hind
contraction
Exp XII
2.00
Control
4.00
Control
accidental
asphyxia
4.30
Control
Animal
killed

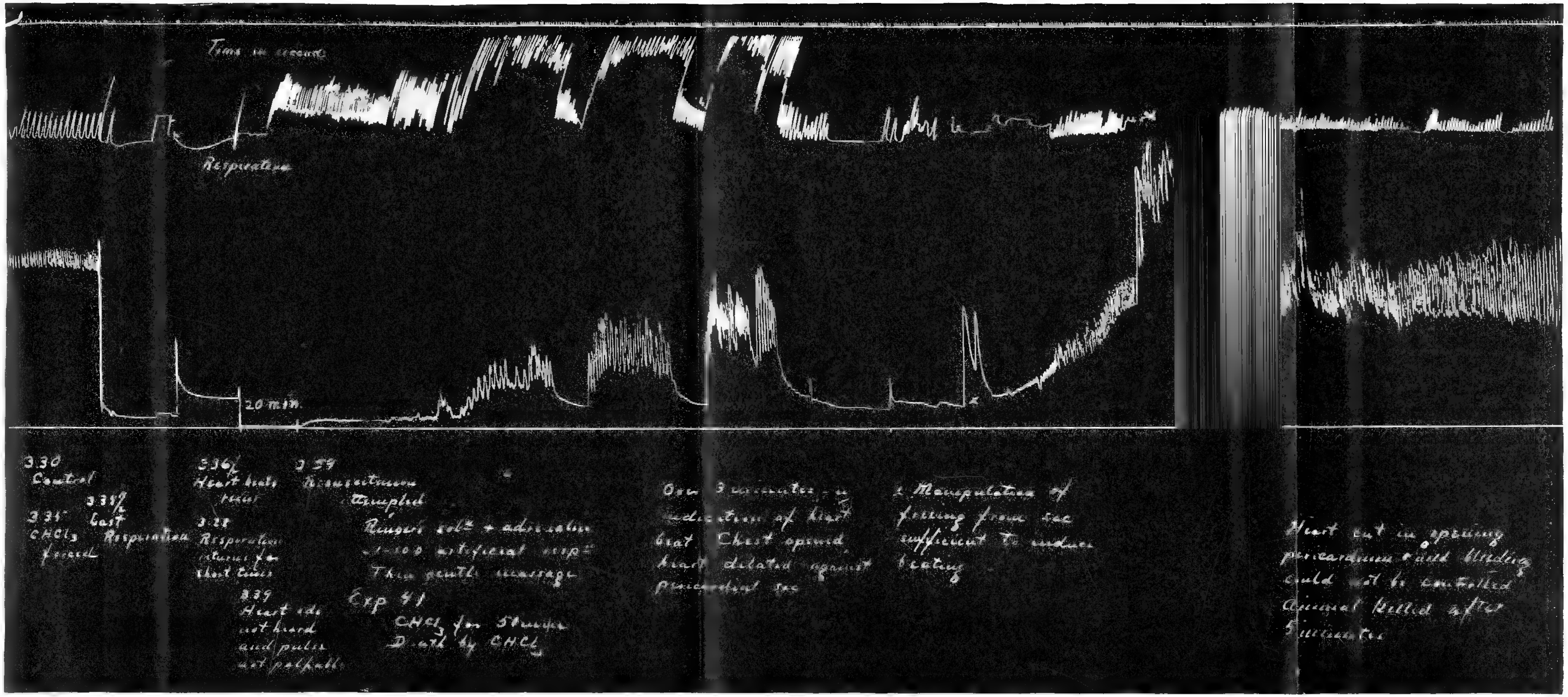
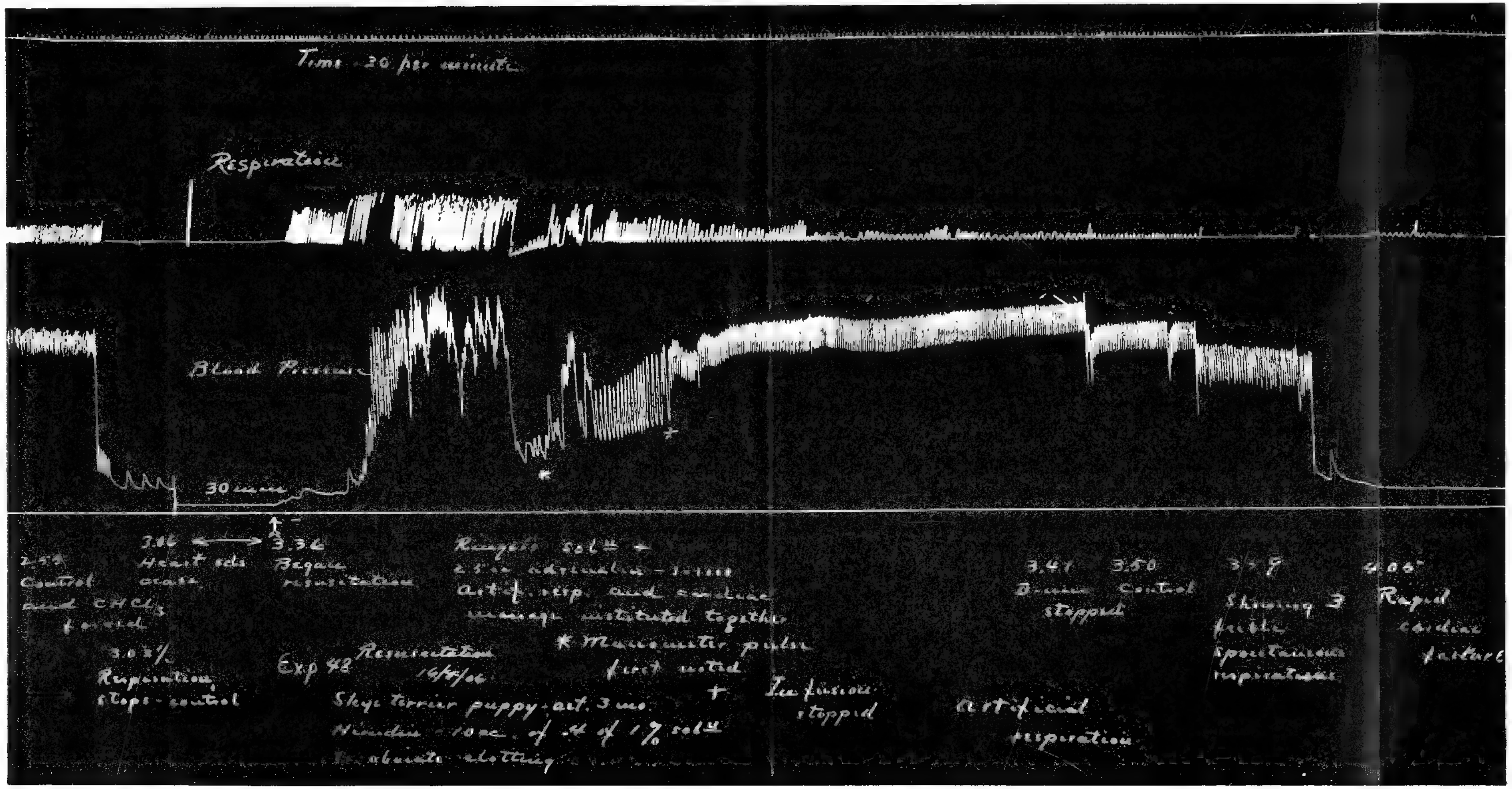
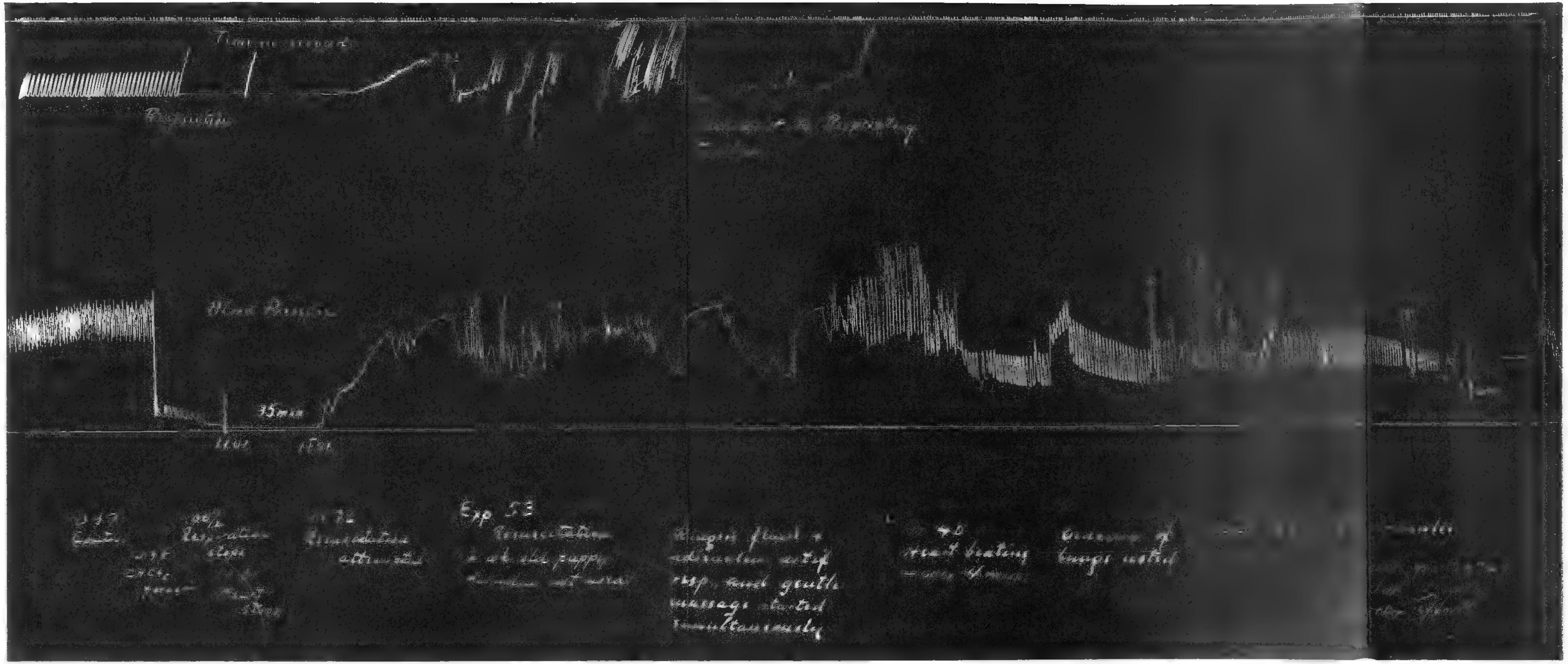

Time in seconds
Respiration
20 mm.
3.30 Control
3.33½
3.35 Last CHCl3 forced
Respiration
3.36½ Heart beats ceased
3.38 Respiration returns for short time
3.39 Heart sds not heard and pulse not palpable
3.59 Resuscitation attempted
Ringer's solⁿ + adrenalin 1-100 artificial respⁿ
Then gentle massage
Exp 41
CHCl3 for 5 mins
Death by CHCl3
Over 3 minutes - no indication of heart beat. Chest opened, heart dilated against pericardial sac
2 Manipulation of freeing from sac sufficient to induce beating
Heart cut in opening pericardium and bleeding could not be controlled
Animal killed after 5 minutes

PLATE XLVIII.




Time in seconds
Respiration
Blood Pressure
35 min
Exp. 53
Respiration
stops
Resuscitation
old puppy
Ringer's fluid +
adrenalin, artif.
resp. and gentle
massage started
simultaneously
Heart beating
Oedema of
lungs noted

3.59—There are three feeble spontaneous respirations which the control shows. These occurred after several attempts to induce them by stopping artificial respirations, burning anus, and pulling on the tongue. Artificial respiration was continued, but the heart began at once to fail.

4.05—Heart stopped beating entirely.

Complete resuscitation within six minutes has been obtained in a number of experiments since the foregoing was sent to press. Later experiments have apparently established the unequal susceptibility for resuscitation of various parts of the brain.

EXCISION OF CANCER OF THE HEAD AND NECK.

WITH SPECIAL REFERENCE TO THE PLAN OF DISSECTION BASED ON ONE HUNDRED AND THIRTY-TWO OPERATIONS.*

GEORGE CRILE, M.D.
CLEVELAND, O.

Though signal advances have been made recently in many surgical problems, the treatment of cancer of the head and neck has, it would seem, neither received the attention nor kept the pace of progress in other fields. These unhappy cases are too often regarded as specters at the clinic. The operative treatment is hampered by tradition and conventionality, and the tragic ending of so large a proportion of these cases has held back lay and even professional confidence.

In this paper it is intended to present an outline sketch of the conclusions regarding the surgical treatment of cancer of the head and neck in the curable stage. The etiology, the diagnosis and the pathology will not be considered. It is generally admitted that cancer is primarily a local disease. Each case, then, is presumably at some period curable by complete excision.

The immediate extension from the primary focus is principally by lymphatic permeation and metastasis in the regional lymphatic glands. Secondary foci in distant organs and tissues are probably due to cancer emboli. A careful study of 4,500 cases, exclusive of the thyroid gland, traced to their original report in literature, made for me by Dr. Hitchings, showed that in less than 1 per cent. have secondary cancer foci been found in distant organs and tissues. That is to say, in cancer of the head and neck, death almost always occurs by local and regional development of the disease. The collar of lymphatics of the neck forms an extraordinary barrier through which cancer rarely penetrates (Figs. 1 and 2). Every portion of this barrier is surgically accessible. Paired organs or distinctly one-sided foci usually metastasize regularly, while unpaired organs, as the tongue, or the mesial tissue, such as the nose and the middle of the lip, metastasize irregularly (Fig. 3).

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* Read in the Section on Surgery and Anatomy of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.

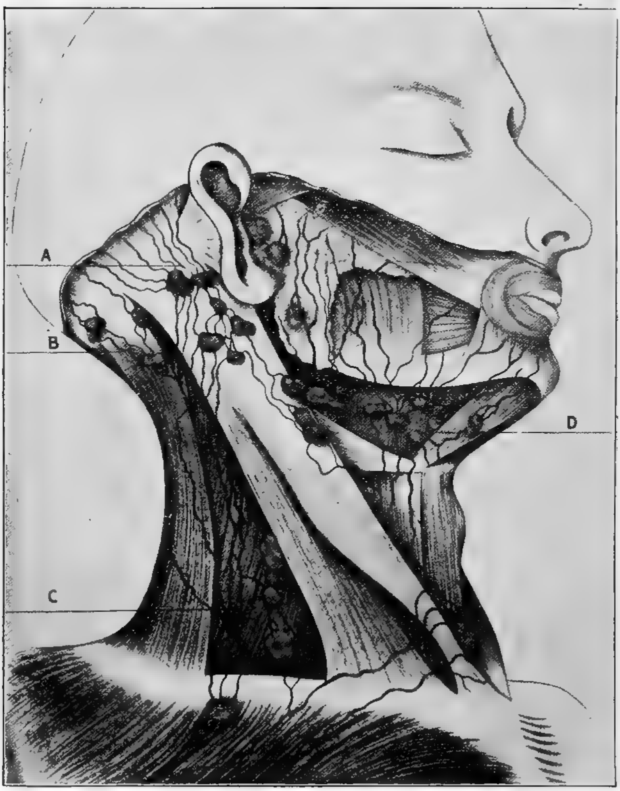

Fig. 1.—(From Gray, Poirier, Cuneo and Toldt.) The distribution of the superficial lymphatics. A, Posterior auricular glands. B, occipital gland. C, superficial cervical gland. D, submaxillary gland.

After the lymphatic stream has been blocked, as by carcinomatous invasion, it may flow in any direction and every sort of irregularity in the further metastases may follow, but always somewhere within the accessible lymphatic collar. After all, how much more favorable such distribution is than that of certain other organs, as, for instance, the breast with its thoracic and abdominal metastases, the stomach and intestines with their inaccessible retroperitoneal metastases?

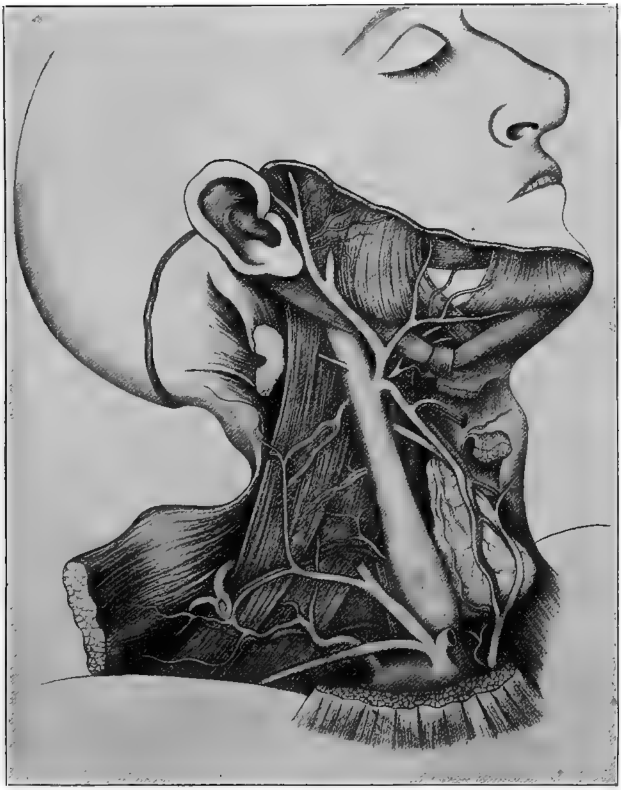

Fig. 3.—(Gray.) **Emphasizing the venous tree, easy to excise in toto but difficult to dissect individually from lymphatics.**

What, then, is the best method of surgical attack? An incomplete operation disseminates and stimulates the growth, shortens life and diminishes comfort. Local excision of the primary focus only is as unsurgical as excision of a breast, leaving the regional glands. Excision of individual lymphatic glands, as one would excise a tuberculous gland, not only does not afford permanent cure, but is usually followed by greater dissemination and more rapid growth. Judged by analogy and experience, the logical technic is that of a "block" dissection of the regional lymphatic system as well as the primary focus on exactly the same lines as the Halstead operation for cancer of the breast. Such a dissection is indicated whether the glands are or are not palpable. Palpable glands may be inflammatory and impalpable

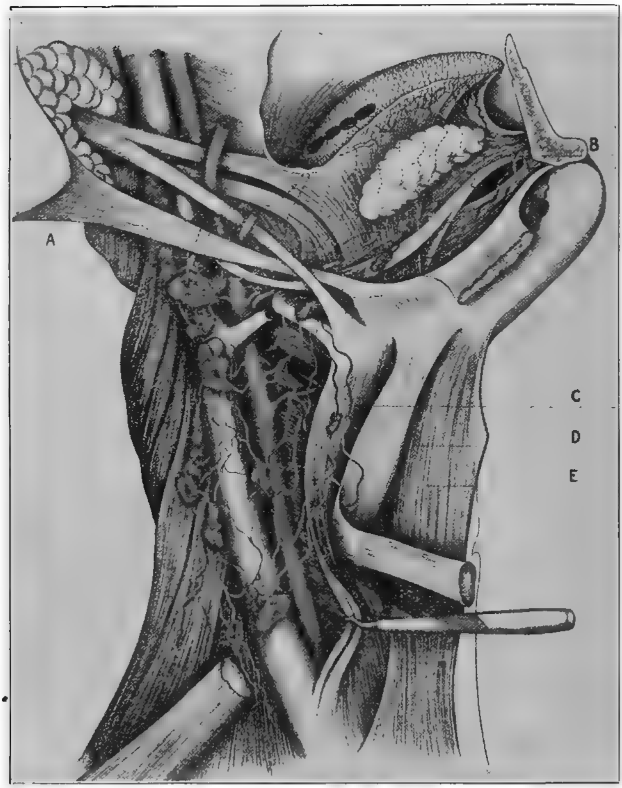

Fig. 4.—(From Poirier and Cuneo.) In cancer of the tongue the metastases extend well down as this cut illustrates. Sometimes the first point of metastasis is in the gland lying between the internal jugular and the omohyoid. A, posterior belly of digastric. B, submaxillary gland. C, thyrohyoid. D, omohyoid. E, sternohyoid.

glands may be carcinomatous. A strict rule of excision should, therefore, be followed (Figs. 4 and 5).

In the last 63 cases we have divided them into two classes: (a) those in which the lymphatics were obviously enlarged, (b) those in which they were not enlarged. The enlarged lymphatics were presumed to be carcinomatous (this was, of course, not always correct). In this group the lymphatic-bearing tissue was widely (the entire lymphatic-bearing tissue of that side) excised, because when once the lymph stream is choked by metastasis further dissemination may travel in any direction. When there are no palpable glands the lymphatic drainage area only is excised.

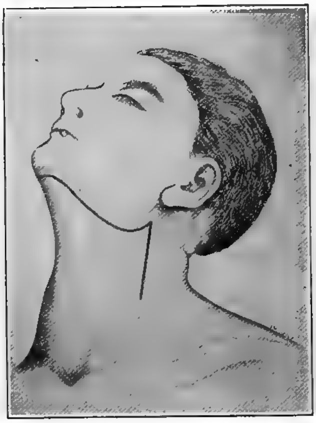

Fig. 5.—An incision which exposes the regional lymphatics which are excised in cases of lateral cancer of the lip without palpable metastases. After metastases have occurred, excision of the entire lymphatic bearing tissue of the side of the neck should be done.

Next in importance to the block regional and local excision is that of a strict avoidance of all handling of carcinomatous tissue so long as the lymphatic channel remains intact, thereby avoiding further dissemination of the growth. Retraction should be entirely on sound tissue and blunt dissection should be the exception.

If the foregoing be mainly true, what, then, are the salient features of the plan and technic, and what are the principal dangers to be avoided? We shall not here consider the preliminary preparation of the patient nor the after-care, but shall address ourselves to the immediate operative problem as to how to secure the highest immediate recovery rate and the most probable permanent cure. What, then, are the immediate dangers attending such operations? Infection, local and broncho-pulmonary, stands first, then hemorrhage, shock and exhaustion.

Infection.—In the present status of surgery, infection may be dismissed without discussion in all clean dissections of the neck in which the wound does not communicate with the mouth, the air passages or the esophagus. The greatest infection risk exists when an extensive dissection wound of the neck communicates with the mouth or air passages, as in cancer of the tongue or of the larynx. In the latter instance experience has emphatically taught us that the primary wound in the neck should not be made at the same time that the larynx is excised. A preliminary tracheotomy is doubly indicated, as, aside from the short circuiting of respiration and fixing the trachea, it produces a wall of protective granulations across the top of the dangerous mediastinal area. After the establishment of this barrier, together with the superficial treatment of the stump of the trachea, but little risk of broncho-pulmonary infection remains.

In the case of the tongue the operation is best made in two stages. It is now well known that the immediate and perhaps the most important factor in the causation of broncho-pulmonary infection in operations within the mouth is the inspiration of blood at the time of the operation. This may be absolutely prevented by the adoption of a simple method which I have heretofore described in the *Annals of Surgery*. The method consists of passing closely fitting rubber tubes through the nares into the pharynx, opposite the epiglottis, then close gauze packing of the pharynx, after drawing the tongue well forward. With the exception of operations requiring the removal of the entire base of the tongue, complete control of blood inhalation is thereby accomplished. Incidentally, this separates the surgeon and the anesthetizer, permitting each to do his work unhampered by the other. Mucus that otherwise might collect in the throat is absorbed at once by the gauze packing. The prevention of vomiting is almost wholly under the control of an even anesthesia. The many other features of the prevention of infection will not here be considered.

Hemorrhage.—The control of hemorrhage is important on its own account and almost equally on account of the maintenance of a dry field, affording opportunity for a clean and precise dissection. The arterial hemorrhage is best controlled by temporary closure of the common or external carotid artery. Permanent closure of the common carotid, on account of the high percentage of cerebral softening in the cancer period of life, should be avoided. Permanent closure of the external carotid, while it is not attended by this risk, carries with it ap-

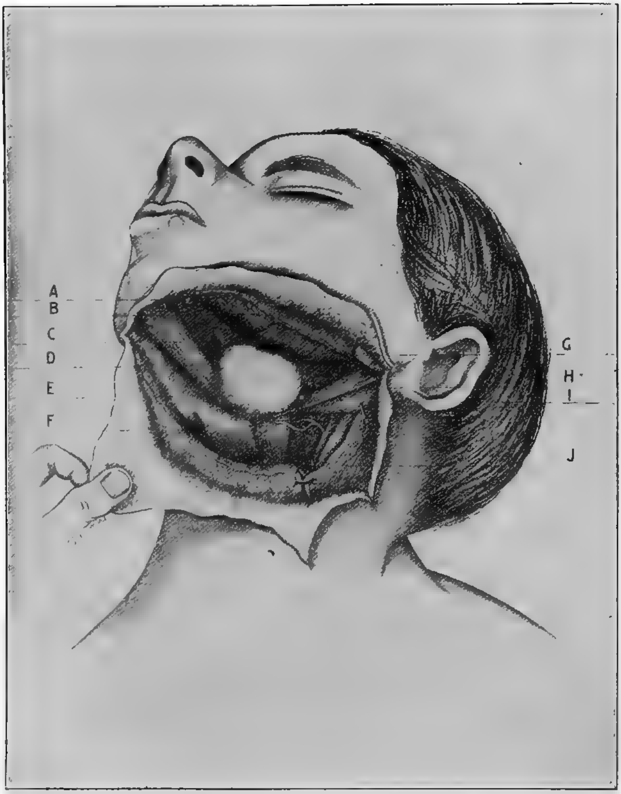

Fig. 6.—(Continuation of Fig. 5.). The regional lymphatic bearing tissue is removed by a block dissection, leaving the salivary gland in the cases in which the lymphatics are free from metastases, and excising it when any of the regional glands are involved. A, submental. B, facial veins and artery. C, gustatory. D, digastric. E, submaxillary. F, platysma. G, parotid gland. H, lingual. I, digastric. J, sternocleidomastoid.

proximately a 2 per cent. mortality rate from the washing away of the thrombus of the ligatured stump, causing cerebral embolism. At all events, it is unnecessary. In 61 cases I have temporarily closed the common or the external carotid without immediate or remote complications. Proper closure of this vessel should be attended with little more risk of thrombosis or embolism than closure by tourniquet or by pressure applied on the skin. This part of the technic must be done with absolute gentleness, the lumen merely closed, the walls not compressed.

The troublesome venous hemorrhage may be minimized by placing the patient in the partial upright posture with a sufficient even pressure on the lower extremities and the trunk up to the costal borders to prevent gravitation of blood. Probably the most convenient means for accomplishing this is by my rubber pneumatic suit. By this device almost any posture may be assumed without serious risk of cerebral anemia by gravity. It is interesting to note the collapse of the veins as the patient is taken from the horizontal to the head-up inclined posture. In atheromatous subjects, presenting a high blood pressure, I have seen marked hemorrhage, even pulsating hemorrhage, from the branches of the external carotid when the common was closed. This is easily demonstrated to be due to the passing of the blood of the opposite artery through the brain, causing a reverse stream through the internal carotid of the clamped side to the bifurcation of the common, then up the external carotid, causing pulsating hemorrhage from the branches of the latter. When this occurs, as soon as the external has been exposed, its lumen may be closed by a clamp, thereby ending the reverse as well as the direct stream of blood.

Shock and Collapse.—In these extensive operations prevention of shock and collapse may be effectively accomplished. The important shock-producing factors are: the number and intensity of surgical contacts, as forcible retraction, vigorous and repeated sponging, blunt dissection, tearing, etc.; the loss of blood; mismanaged anesthesia, and the duration of the operation. The principal factors causing collapse are: interference with the trunk and certain branches and terminals of the vagus, excessive hemorrhage, air emboli and anesthetic accidents.

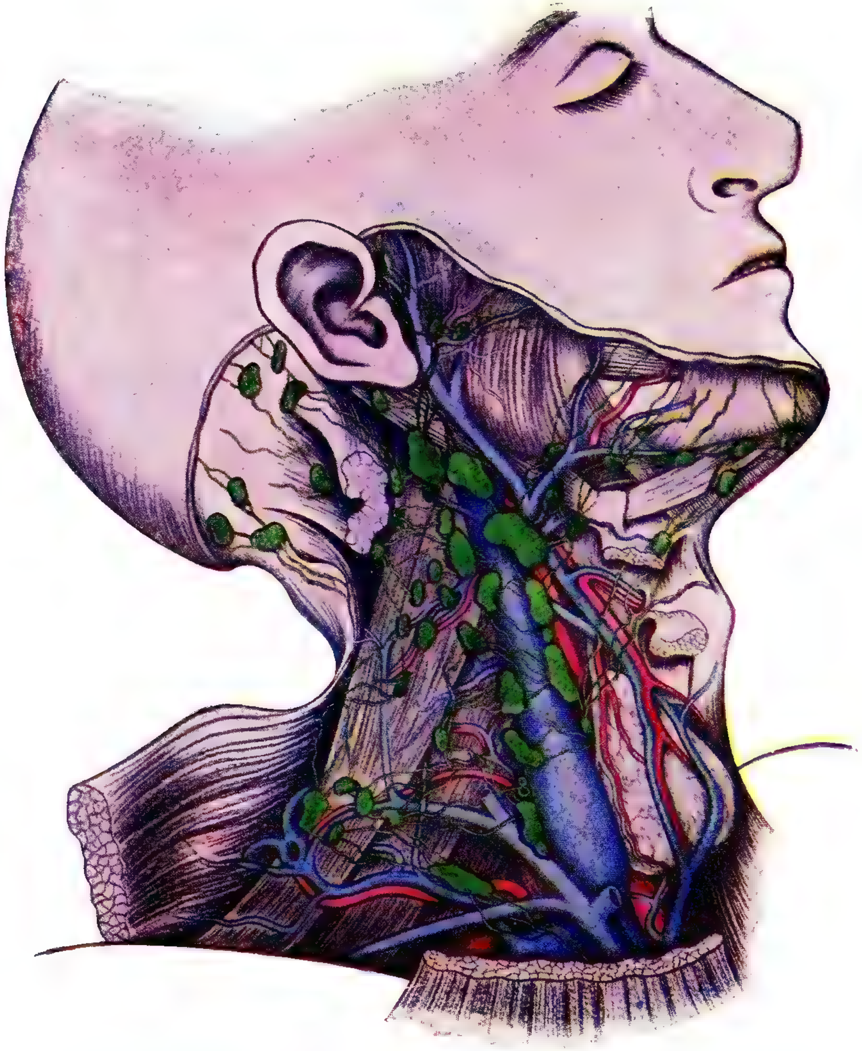

Fig. 2. (Modified from Gray and Cuneo.) The intimate relationship between the venous and the lymphatic systems and the difficulty of entirely excising the lymphatic system and leaving the venous intact. Also how easily both may be excised together.

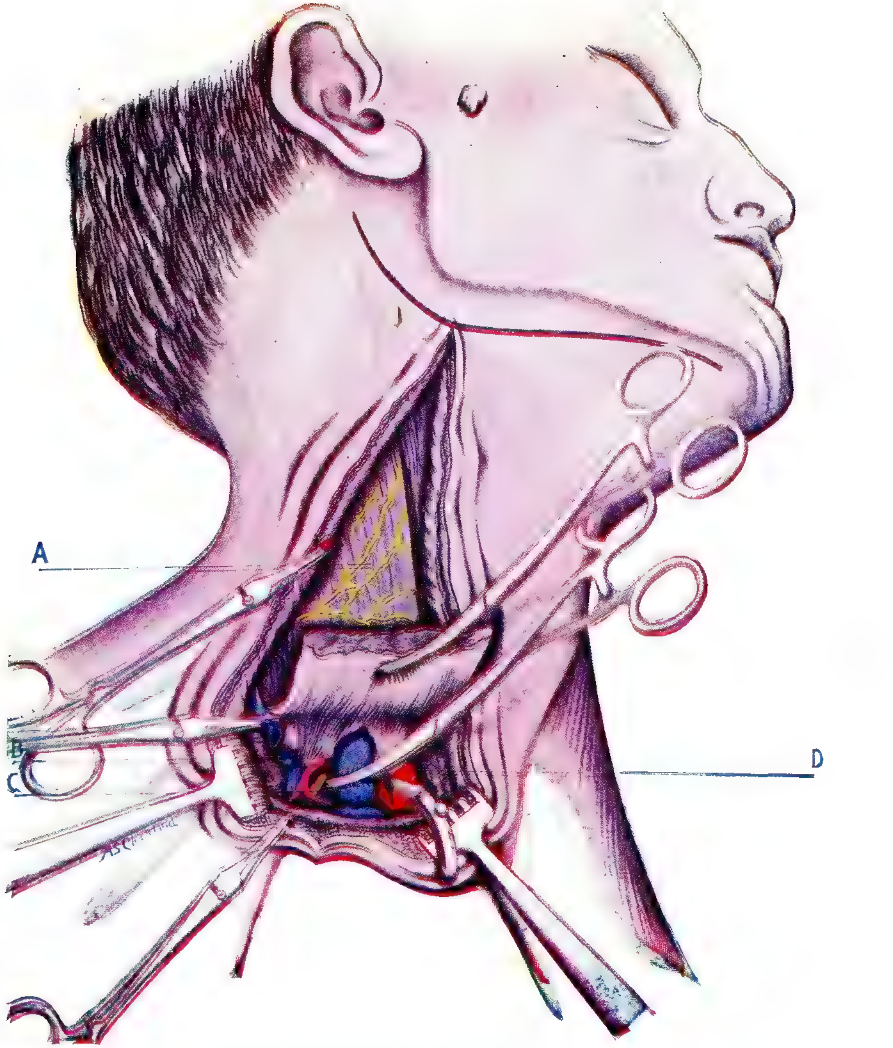

Fig. 10. The sternomastoid is divided near the clavicle. The vein is exposed, tied in two places, and divided. The carotid is closed with the author's special clamp. The skin and platysma are then dissected back on the entire side of the neck. The deep plane of the neck down to the region having no lymphatic gland tissue is opened from below and laterally upward, and the relation of the sternomastoid muscle and the cervical fascia is noted. The most complete exposure of the deep lymphatics is afforded by a complete excision of this muscle. This and the following cut suggest again the necessity of doing a dissection in planes parallel to the surface. A, sternocleidomastoid. B, external jugular. C, internal jugular. D, common carotid.

To minimize the foregoing, the operative field should be subjected to the very minimum trauma by the employment of ample operative space, sharp dissection, minimum retraction, by preserving the field free from blood and minimizing the sponging. The loss of blood may be reduced to a minimum by methods already suggested. A hypodermic injection of atropin is given half an hour before beginning the operation for the purpose

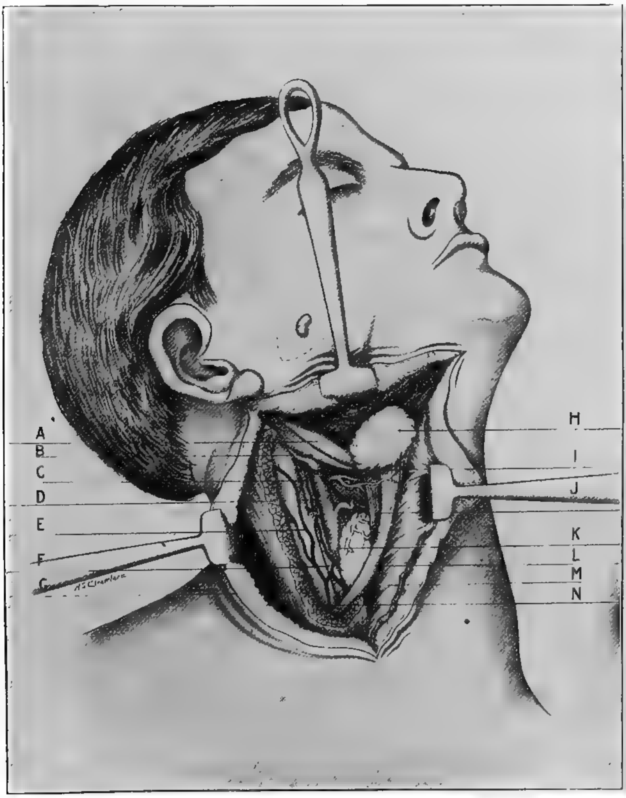

Fig. 7.—Drawing from a case of epithelioma of the face near the ear. There were no palpable glands. The local block dissection here included a portion of the sternomastoid so as to afford a better exposure of the parotid group of glands, thereby protecting against injury of the facial nerve or the jugular. In this instance the lower part of the parotid gland was excised. The submaxillary was left. A, sternohyoid. B, digastric. D, internal carotid. F, carotid. G, sternocleidomastoid. H, submaxillary gland. I, hypoglossal. J, thyrohyoid. K, external carotid. L, omohyoid. M, platysma. N, internal jugular.

of paralyzing the nerve endings of the vagus in the heart, thereby wholly preventing an inhibitory collapse from direct or reflex inhibition through the vagus or its branches and controlling bronchial secretion. Morphin favors quiet anesthesia and partially supplements the general anesthetic. By taking advantage of the distribution of the sensory nerves, the supply of which is rich in the skin and superficial fascia while scanty in the deeper planes of the neck, but little ether, in addition to the morphin, is required during the latter dissection. This is analogous to the ether-morphin anesthesia in certain prolonged abdominal technics, in which the less painful part of the operation is done principally under the morphin factor of the anesthetic alone. The factor of hemorrhage may now be practically eliminated, and with it air embolism.

In operations on the tongue it is well to remember that the lingual arteries may be closed by the firm pressure of the gauze packing at the base of the tongue in the technic of tubage. In neck dissections the desired standard of the technic is attained when the field is so clear that the minute tissues, such as individual lymphatic vessels, are clearly and distinctly seen, and when one would not expect to damage even the sympathetic nerve unintentionally.

In estimating the possible shock, collapse or exhaustion, it is well to bear in mind that in the cancer period of life there are apt to be cardio-vascular changes of importance. A high degree of atheroma, a senile heart, or a chronic myocarditis are all important factors which should be met before the day of operation by such therapeutic measures as digitalis, nitroglycerin, etc., as may be indicated. Unless these factors are anticipated but little can be done in the midst of an operation toward their mitigation. When the wound is large, one must not forget the importance of moist saline compresses to prevent the effect of exposure to the air.

The practical application of the foregoing data may be illustrated in the technic for the excision of carcinoma of the floor of the mouth invading the lower jaw with extensive metastases in the submaxillary lymphatic glands. In this instance one would be compelled to take the double risk at one seance. Assuming all preliminary preparations to have been made, the patient is given an injection of 1/4 morphin and 1/100 atropin half an hour before beginning of anesthesia. After completion of anesthesia the pharynx is cocainized to prevent reflex inhibition from manipulation; two rubber tubes closely filling the nares and having perforations at the distal end are pushed down to the level of the epiglottis,

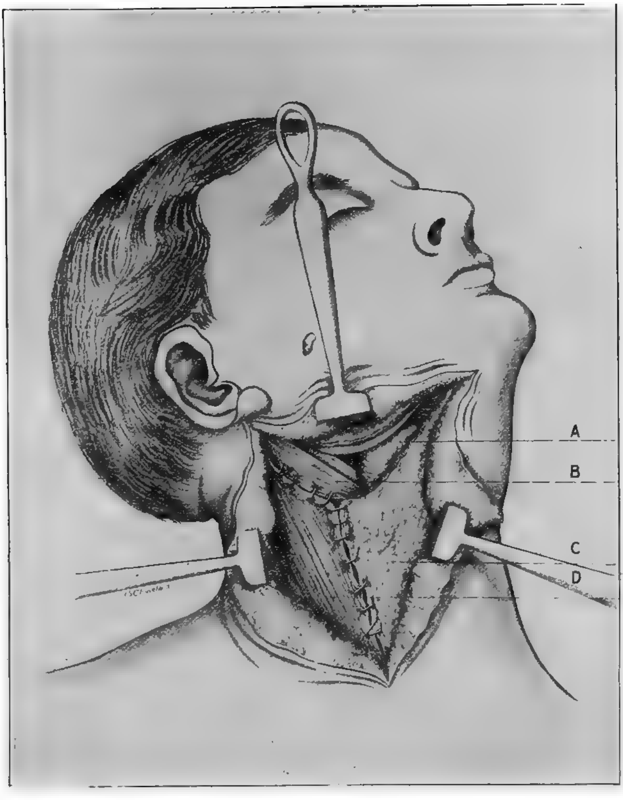

Fig. 8.—(Continuation of Fig. 7.) A method of closing the deeper plane of the neck by suturing the longitudinally split border of the sternomastoid to the platysma and the digastric. A, sublary gland. B, posterior belly of digastric. C, platysma. D, sternomaxillary gland. B, posterior belly of digastric. C, platysma. D, sternomastoid.

the tongue is then drawn well forward, a large piece of gauze packed firmly into the pharynx, completely filling it, the brunt of the packing being made at the sides of the tubes, preventing their compression; the patency of the tubes and easy respiration is readily verified; a T-tube is then connected up with an inhaler and the anesthetizer takes his place a foot or more from the field of operation, giving him the opportunity of continuing an even, uninterrupted anesthesia, allowing the surgeon full control of the operative field, absolutely preventing the entrance of any blood into the pulmonary tract, and permitting the operator to place the patient in any position he wishes.

The rubber suit has been placed and laced during the administration of the anesthetic, and is now sufficiently inflated to merely support the circulation of the extremities and the abdomen up to the costal arches. The patient is then placed in the inclined posture, head up, and the skin incision over the common carotid artery just above the clavicle is made (Fig. 6). The artery is exposed by an intermuscular separation of the sternomastoid, its outer sheath nicked, the vessel exposed and temporary closure made. The complete skin incisions are then made, the skin reflected back over the entire area of the field. The sternomastoid is divided, the internal and the external jugulars are secured, tied double and divided at the base of the neck (Fig. 7). The dissection is then carried from below upward into the deep plane of the neck behind the lymphatic glands, working first at the sides, then posteriorly, carrying upward all the fascia, muscles, veins, fat and connective tissue until the floor of the mouth is reached (Fig. 8). The lower jaw is then divided at a safe distance on each side of the growth. The floor of the mouth and the border of the tongue are then similarly divided, completing the block.

In very critical cases, an assistant experienced in the use and purpose of the sphygmomanometer is placed in charge of the management of the circulation. If the pressure falls below a certain point the pneumatic pressure is increased, and after the operation the suit is gradually decompressed, but in operations in the mouth in which there may be some oozing, and in which the posture of the patient may measurably prevent inhalation of blood, by continuing the rubber suit the patient may be allowed to come out of the anesthetic in the head-up posture. The pneumatic suit may be gradually decompressed after the circulation has reached a safe physiologic status.

Clinical.—My experience consists of 132 operations for cancer of various parts of the head and neck. A

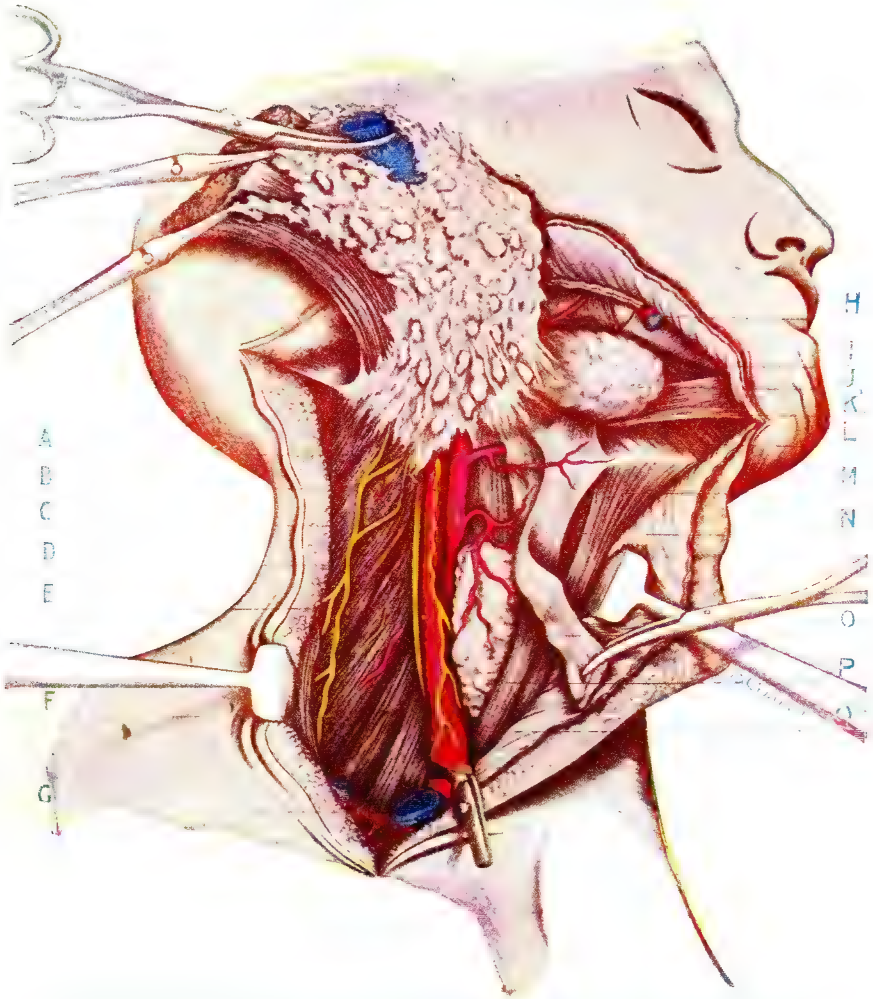

Fig. 11.—The entire mass of lymphatic gland bearing tissue is excised *en bloc*, and handled as little as possible. This dissection becomes easy when followed in the deep plane. The entire block of tissue is finally divided above, including the vein. A, splenius. B, hypoglossus descendens. C, spinal accessory. D, elevator ang, scapuli. E, pneumogastric. F, scalenus posticus. G, internal jugular. H, facial vein and artery. I, submental. J, submaxillary, K, digastric. L, mylohyoid. M, sternohyoid. N, omohyoid. O, thyroid gland. P, thyrohyoid. Q, carotid.

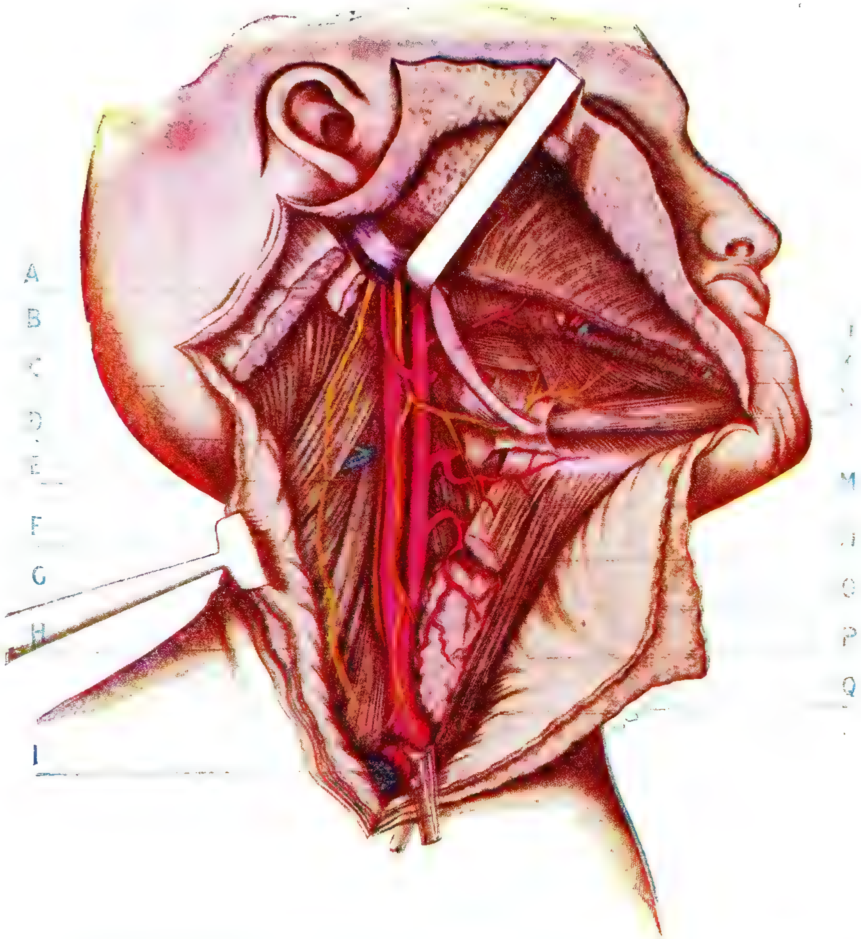

Fig. 12. (Drawn from life.) Complete block excision of the regional lymphatic system. Note complete removal of all tissue lying between the platysma and the deep muscular plane in which no lymphatic glands lie. The artery and nerves remain. The excised block includes fascia, fat, salivary and part of the parotid glands, sternomastoid, omohyoid, part of the stylohyoid, the entire venous system, and all the lymphatic vessels and glands in this region. This is quite as comprehensive and complete as the Halstead excision of the breast. A, digastric. B, sternocleidomastoid. C, spinal accessory. D, splenius. F, elevator anguli scapuli. G, pneumogastric. I, internal jugular. J, stylohyoid. K, mylohyoid. L, digastric. M, omohyoid. N, sternohyoid. O, platysma. P, thyroid gland. Q, carotid.

study of the literature convinces me that one could obtain the safest conclusions from his own experience, as it is impossible to get a precise knowledge of the plan. purpose and descriptions of the work of other surgeons. I have, therefore, depended largely on my own tables for my conclusions.

In the first part of this series we now appreciate as we could not then, that incomplete operations do more harm than good. Our principal errors on this point consisted in the removal of individual glands, in allowing insufficient space for the dissections, in regarding hemorrhage too lightly, in handling carcinomatous tissue, in limiting the dissection only to tissues known to be infected; in short, in not doing a complete, comprehensive operation. The early and vigorous return growth clearly proved the fallacy of our technic. Experience, too, more clearly taught us what cases should be considered inoperable. We have never seen benefit from excising a recurrent malignant tumor which had transgressed lymphatic glands and freely invaded the deeper planes of the neck. If, on the other hand, the deep planes were free and the skin involved, there still remained hope of cure.

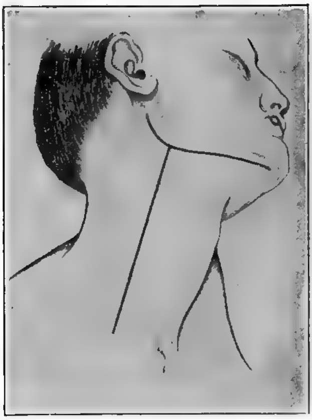

Fig. 9.—Skin incision for block excision of the gland bearing tissue of the entire side of the neck. A procedure always done when glands are involved.

Superficial epitheliomata in aged subjects, appearing on various parts of the skin of the face, usually about the nose, rarely metastasize. The block dissection when done in cases in which the lymphatic glands of the neck are already involved, is most radical. In all these the key to the situation is the complete excision of the internal jugular vein (Fig. 2). In one case both the internal and external jugulars of one side were excised their whole length from the bottom to the top of the neck; when, several months later, metastasis appeared on the opposite side of the neck, a similar excision of both veins was made on this side also, but only after it was discovered what the compensating route for the return circulation was. It was found that some of the superficial branches of the jugular had assumed the size of the internal jugular and were evidently the principal veins of compensation. Following the excision of the internal and external jugulars of the opposite side of the neck there was not the slightest circulatory disturbance, congestion, or any hint of insufficient return circulation (Fig. 9).

Since the adoption of the plan and practice as here described, in 1898-1899, we have seen most encouraging results not only in the immediate recovery rate, but in the permanent cures. We have now apparent cures in patients in whom at the time of operation, various stages of cervical metastases were demonstrated. Among them was a case that was so large and so extensively involved the skin that the patient's physician lanced it, supposing it to be an abscess. This has passed the three-year period. Better selection of cases and improved technic have materially reduced the immediate mortality rate.

It is not intended here to assume that all cancers in the various tissues of the head and neck are alike curable, but when once the lymphatics of the neck are involved the surgical problem and the risk are independent of the location of the primary lesion.

SUMMARY OF AUTHOR'S OPERATIVE CASES.

NUMBER OF CASES, 132.

Age.

Mean age 50, youngest 28, oldest 77; 90 observations.

Cases between ages of 20 and 30 years	1
Cases between ages of 30 and 40 years	14
Cases between ages of 40 and 50 years	21
Cases between ages of 50 and 60 years	18
Cases between ages of 60 and 70 years	29
Cases between ages of 70 and 80 years	6

SEX AND SOCIAL STATE.

Females, 15; males, 96. Married, 40; single, 10.

LOCATION OF PRIMARY FOCUS AND IMMEDIATE RESULTS.

Location.	Operations.	Recoveries.	Deaths.
Epithelioma lateral margin eye	6	6	0
Carcinoma of face (including maxillæ)	15	14	1
Carcinoma of lips	31	31	0
Carcinoma of floor of mouth	4	1	3
Carcinoma of soft palate	1	1	0
Carcinoma of alveolar process	2	2	0
Carcinoma of pharynx	1	1	0
Carcinoma of tongue	12	10	2
Carcinoma of tonsil	2	2	0
Carcinoma of nose	5	5	0
Carcinoma of scalp	2	2	0
Carcinoma of lymphatic glands	23	20	3
Carcinoma of parotid	5	5	0
Carcinoma-branchiogenic	4	4	0
Carcinoma of larynx	15	13	2
Carcinoma of thyroid	4	4	0
	132	121	11 8 per cent.

OTHER DATA.

Mean duration of disease prior to operation, 1 year. In the last 21 operations there has been no fatality.

Total number of cases operated	132
Total number of cases traced	106
Number of these known to be living	47
Number of these that did not have radical block dissection.	96
Number of these operated over 3 years ago	67
Number of these traced	48
Number who have passed 3 years	9
Number of radical block dissections	36
Number of block dissections over 3 years	19
Number of these traced	12
Number of block dissections of patients living who have passed the 3 year period	19

0 to 1 year	5	6 to 7 years	1
1 to 2 years	5	7 to 8 years	0
2 to 3 years	0	8 to 9 years	0
3 to 4 years	2	9 to 10 years	0
4 to 5 years	2	10 to 11 years	1
5 to 6 years	3		

Number that did not have block dissections now living....28

0 to 1 year	6	4 to 5 years	3
1 to 2 years	10	5 to 6 years	2
2 to 3 years	3	7 to 8 years	3
3 to 4 years	0	16 to 17 years	1

There were twenty-three operations for cancer metastases in the cervical lymphatics following operations for the excision of the primary focus alone. Some of these were in my own early cases in which I was led to excise only the primary focus, either by the pleading of the patient or because the trifling primary lesion scarcely seemed to warrant excision of the regionary lymphatics (Figs. 10 and 11). The majority have been drawn from other sources. It would seem that the end results in this class of cases are the real test of the effectiveness of any method. The end results here are certainly equal to that of cases of axillary involvement in breast cancer. Increasing experience confirms us more and more in the belief that there has been too much conventionality in the technic. The evolution of the technic has so much minimized the operative risks that the chief consideration at present may be given to the complete excision of the last vestige of the disease along the lines of the principles underlying operations for cancer in general.

I would direct especial attention to the fact that among the 48 traced cases operated on more than three years ago, in which the radical block dissection was not made, nine are living; while among 12 traced cases among the block dissection cases operated on more than 3 years ago nine are living. The radical block dissection has, therefore, shown itself to be four times more effective than the less radical (Fig. 12).

Our general conclusions are that, since the head and neck present an exposed field, cancer here, unlike that of the stomach, the intestines, or even the breast, may be recognized at its very beginning; that every case is at some time curable by complete excision; that the field of regional metastases is exceptionally accessible; that cancer rarely penetrates the extraordinary lymphatic collar of the neck; that the growth tends to remain here localized; that by applying the same comprehensive block dissection as in the radical cure of breast cancer and by freely utilizing the modern researches of surgery the final outcome in cases of cancer of the neck and head should yield better results than that of almost any other portion of the body.

Reprint from SURGERY, GYNECOLOGY AND OBSTETRICS, July, 1906

Western Reserve University
Department of Surgery

REPORT OF CASE OF MULTIPLE GIANT-CELLED SARCOMA

By GEORGE W. CRILE, M. D.
Associate Visiting Surgeon, Lakeside Hospital
AND
W. C. HILL, M. D.
Radiographer to Lakeside Hospital

CASE 6155. Female, age 22. Tumor found in the right tibia, left femur, body of the fifth dorsal vertebra, both hands, and forearms. Operation on the right tibia. Removal of the tumor by means of a bone curette. Recovery from the operation, later spontaneous fracture of the left femur. Patient in apparently good health at present.

Complaint. Patient had been for several months suffering from pain in the upper portion of the right tibia and in the lumbar and dorsal vertebræ. The pain was progressive, finally becoming so severe as to cause serious disability.

Family History. Father living and well; mother died of tuberculosis seventeen years ago. Two brothers living and well. Father has had diabetes. Mother had syphilis.

Personal History. Did not have the ordinary diseases of childhood; has always been well and active; is a talented musician. She has had a chronic discharge from the right ear since childhood. No evidence of acquired syphilis.

Present Illness. About a year ago had aching pains in arms and legs, in the left side, and in the lower dorsal and upper lumbar region. This continued to increase until she became quite invalided. A year ago a lump appeared over the right tibia. Seven months ago a similar one appeared over the spine, at the level of the scapula. At the time of her entrance to the hospital, there was a swelling in the hard palate. These points were painful, but the pain was not so marked as it was in the beginning.

Physical Examination. Patient of medium size. Some papillary eruptions on back, and slight swelling in roof of mouth. No deformity of spine, but there is tenderness at the lower border of scapula. No general glandular enlargement. Reflexes very active. At middle crest of right tibia a slight swelling.

Diagnosis. X-ray examinations revealed definite tumor-like masses, the most marked one being in the upper portion of the right tibia. She had been under specific treatment, but showed no improvement. Largely as a diagnostic measure, the right tibia was opened, the tumor removed with bone curette, and submitted to Dr. W. T. Howard, Jr., for pathological examination. Sections showed areas very closely resembling giant-celled sarcoma.

Operation. Incision was made over the middle third of the tibia, over the tumor, and portion of the bone chiseled out. The new growth and necrotic portion of bone was then separated and lifted out in a mass. The remainder of the bone cavity was then thoroughly curetted with a bone curette, wound packed open with iodoform gauze, and moist dressings applied.

The patient bore the operation well, but the lesion of the bone was slow in repairing. The patient was then given iodide of potassium to saturation, during which time the wound healed rapidly. The patient was given a brace to relieve her back on leaving the hospital. At the time of discharge from the hospital there was no pain, and the patient had increased in weight and general health.

Four months later there was a return of the pain in the dorsal region and a new pain in the left thigh. She was re-admitted to Lakeside Hospital for further observation. The entire bony skeleton was then systematically searched with the X-rays by Dr. Hill for the discovery of any beginning lesions. As a result of that examination there were found distinct foci in the right ulna, right os magnum, the right metacarpus of the middle and index fingers, the second phalanx of the middle

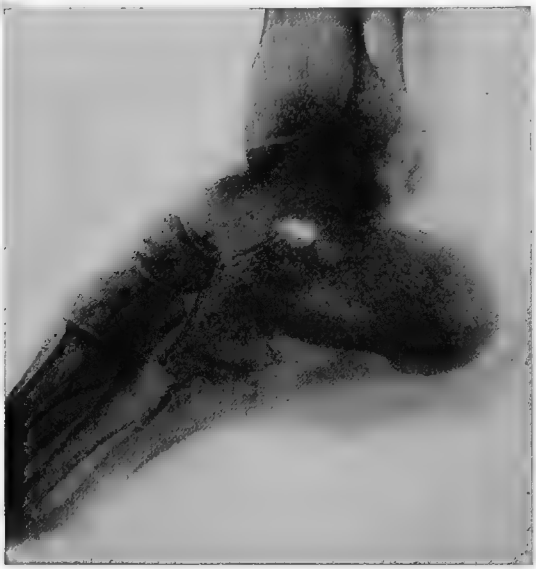

Plate 1. Right foot. Focus in outer malleolus.

finger, the left trapezoid, the left metacarpus of the middle and ring fingers, the left first phalanx of ring-finger, middle third of left ulna, upper end of right ulna, many foci in the middle and lower thirds of the left femur, small focus in the right, in right upper malleolus, the right outer side of head of fibula extensive involvement of the shaft of the right tibia, and in the right side of the fifth dorsal vertebræ. The patient has within the last month been complaining of pain in the right thigh. Previous attempts to locate foci by the X-ray have been unsuccessful, but Dr. Hill has succeeded in finding two which show in Plate 8.

These foci are characterized by their appearance in the medullary portion of the bone, usually well defined, sometimes very small, sharply circumscribed, at other times elongated, appearing either in the epiphysis or in the shaft, in the short bones more often than in the epiphysis.

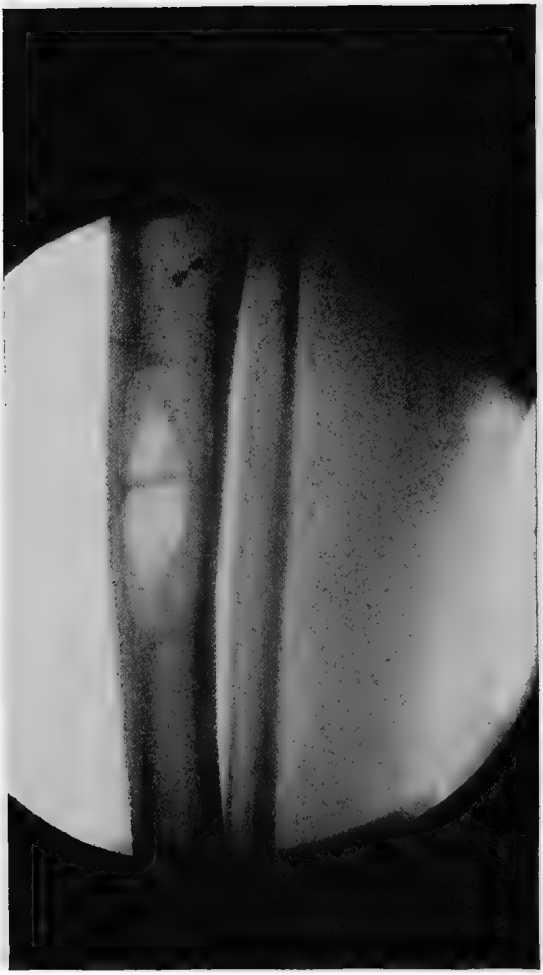

Plate 2. Right leg. Focus in middle third of tibia.

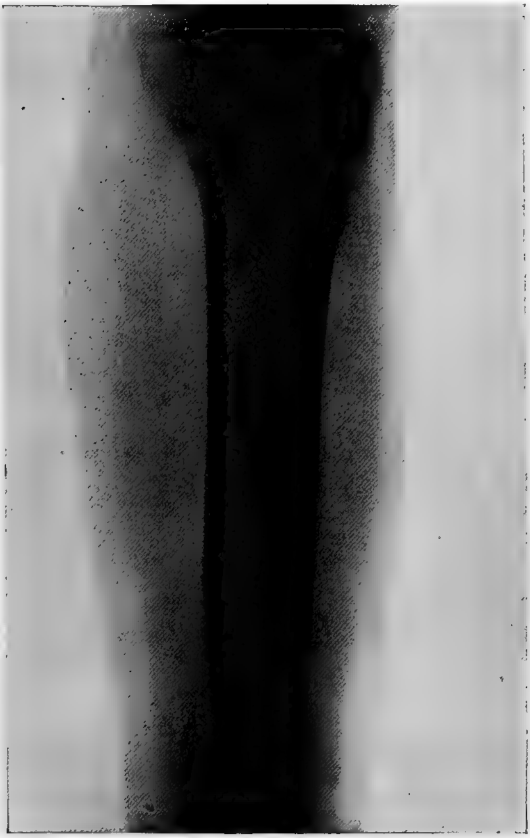

Plate 3. Right leg. Focus in outer side of head of fibula. Extensive focus of shaft of tibia.

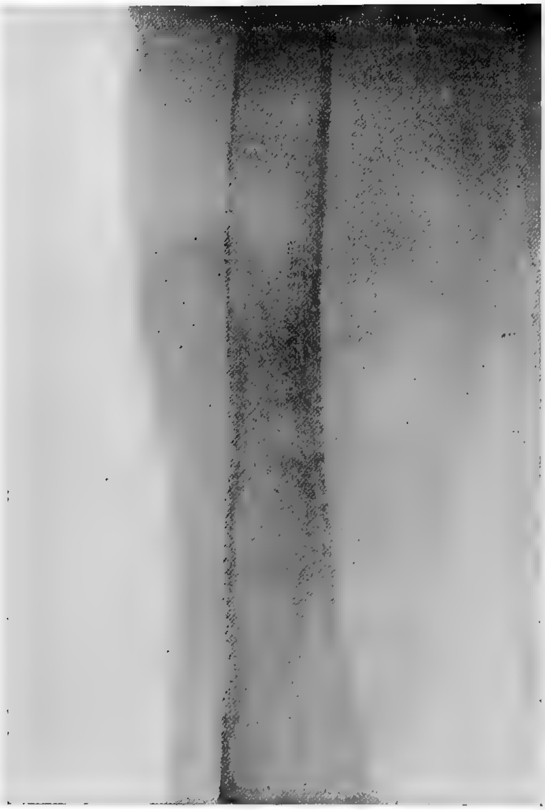

Plate 4. Showing foci in right femur.

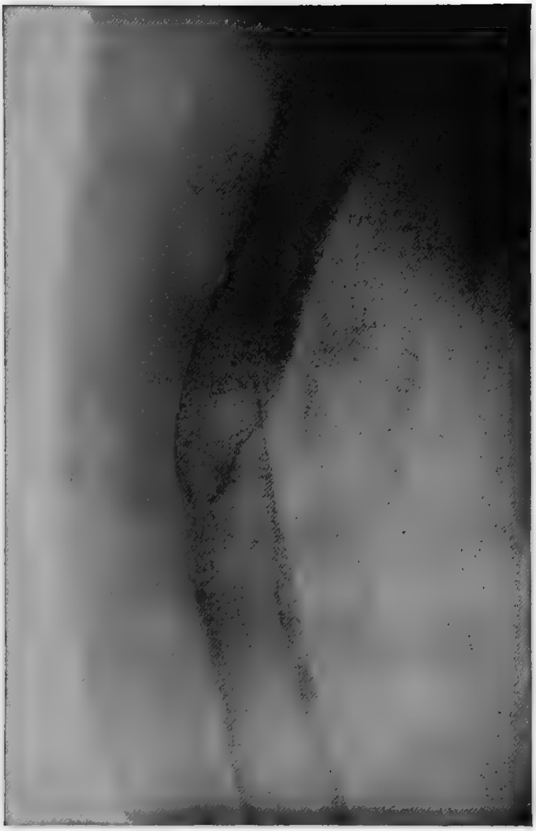

Plate 5. Left thigh. Spontaneous fracture through seat of tumor.

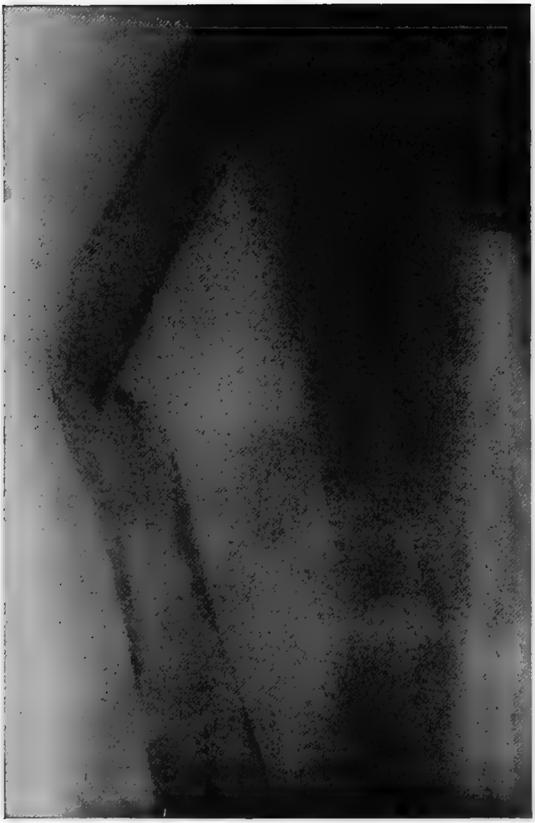

Plate 6. Left thigh. After removal of plaster cast. Shows some attempt at union. Foci in lower third more marked than in Plates 1 and 4.

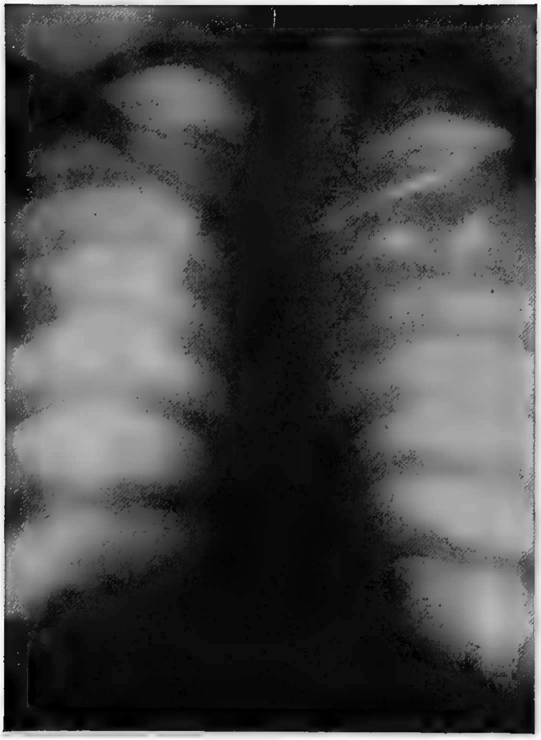

Plate 7. Spine. Fourth and fifth dorsal vertebræ involved; disease especially marked in right side of fifth dorsal. Small foci in fourth and fifth ribs, about 6 cm. from spine.

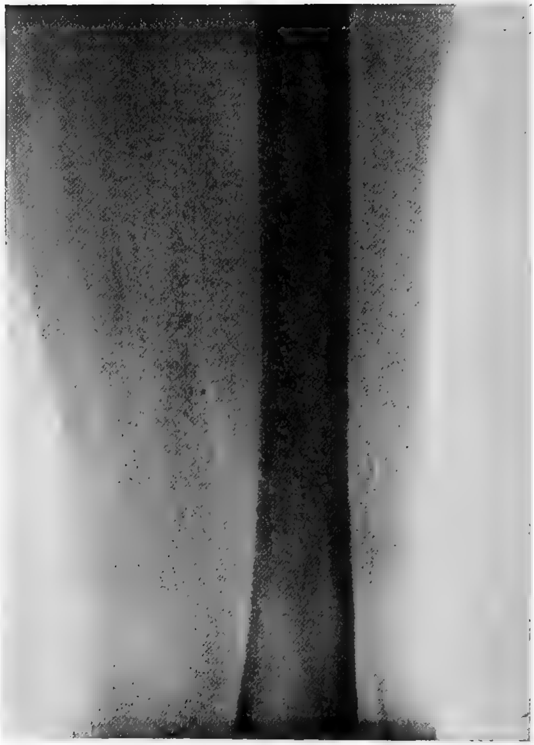

Plate 8. Right femur. Diffuse focus in the lower third. Definite small focus in middle third.

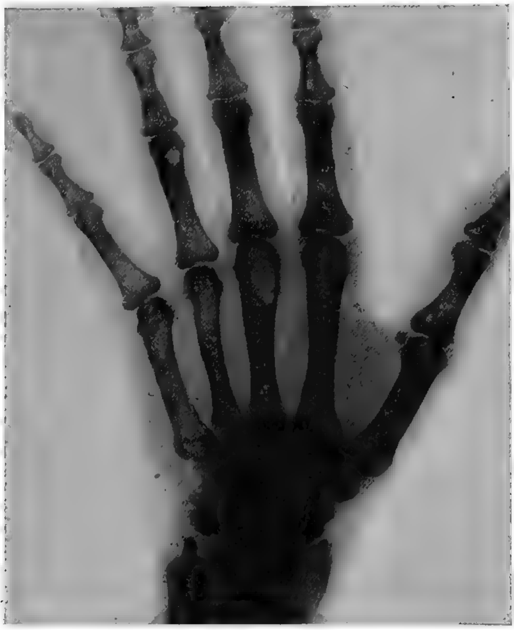

Plate 9. Left hand. Foci in trapezoid, the metacarpals of middle and ring fingers, and first phalanx of ring-finger.

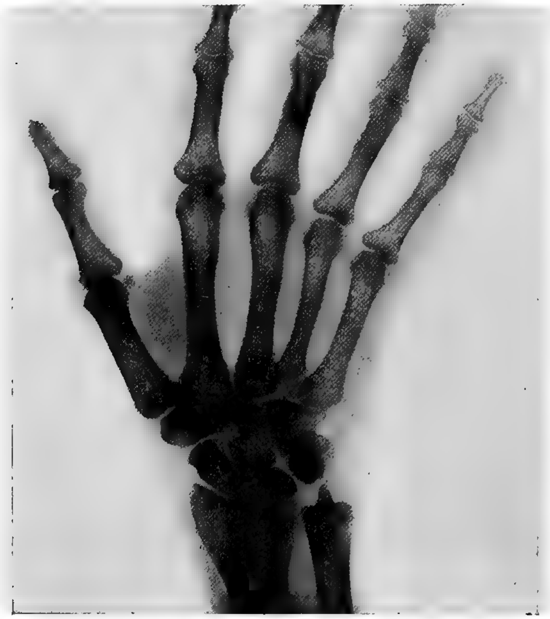

Plate 10. Right hand. Foci in ulna, os magnum, metacarpals of middle and index fingers, and second phalanx of middle finger.

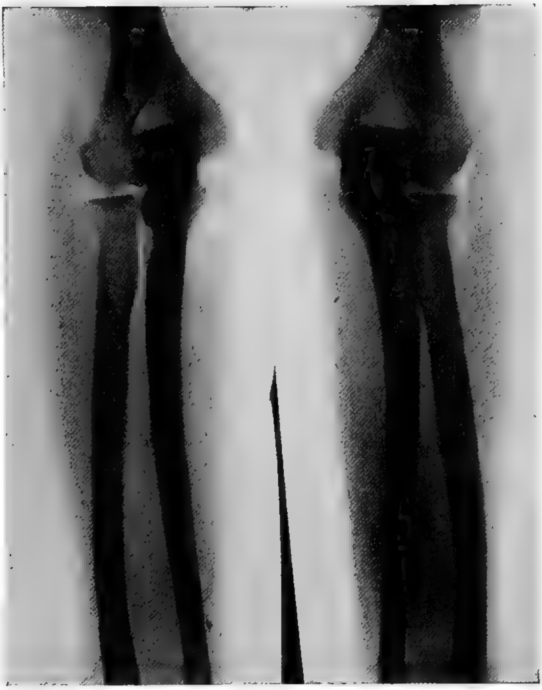

Plate 11. Forearms. Small focus in middle third of left ulna. Focus in upper end of right ulna.

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A CONTRIBUTION TO THE KNOWLEDGE OF ENDOTHELIOMA AND PERITHELIOMA OF BONE.

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INTRODUCTION.—From time to time there have been reported cases of bone tumor showing certain peculiarities of structure which have served to separate them from the ordinary osteo- and periosteal sarcomata on the one hand, and the peculiar tumors or group of tumors classified as myeloma on the other. Such cases were reported in the sixties by Lücke, Kocher, and Billroth; in the seventies by Engelmann, Jaffé, Sudhoff, and others. To Hildebrandt (1891) belongs the credit of collecting these cases from the literature and giving a clear clinical and pathological picture of this affection. His work was based on eight cases, including one of his own. Volkmann (1895), in his exhaustive article on endothelial tumors in general, reported a case of endothelioma of bone, abstracted the previously reported cases, and analyzed the tumors according to their seat and histological structure. Volkmann's conclusions were based upon fourteen cases, one of which (Zahn's second) was evidently a myeloma and should be excluded. Including our own four cases, herewith reported, there are now twenty-three cases available for analysis and generalization. The present work consists in (1) An abstract of the previously reported cases. (2) Report of four new cases. (3) Pathology of endothelioma and perithelioma of bone; (*a*) general pathology; (*b*) histology; (*c*) histogenesis. (4) Etiology. (5) Clinical history, diagnosis, and treatment.

The following cases classed as endothelioma or perithelioma primary in bone are to be found in the literature. The earlier ones have been already collected in the articles of Hildebrandt, L. Volkmann, and Gaymard, but they have not appeared in English:

CASE 1.——LÜCKE, 1866, reported the case of a woman forty years of age, who complained of lancinating pains and a swelling in the right arm, and on reaching to a high place developed a spontaneous fracture. An elastic tumor rapidly developed. The axillary glands were not invaded. Disarticulation at the shoulder; no recurrence after three and one-half years.

Tumor.—The tumor was covered with healthy skin and atrophied muscle. On section it was soft, of a red color, and contained a large cavity filled with bloody fluid. Microscopically there was a fine reticulum with blood-vessels, supporting bands, and gland-like columns of epithelial-like cells, many of which contained colloid material.

Origin in the marrow cavity.

CASE 2.—KOCHER, 1868, a male, aged sixty-six years, eight months after an injury developed a pulsating tumor, with a systolic bruit, of the frontal and temporal bones.

Under the impression that it was an aneurism the carotid was ligated. Pulsation disappeared but returned, when the growth was extirpated.

The tumor developed between the pericranium and the dura. Microscopically the tumor was very vascular and contained spaces lined with rows of cells and containing blood in their lumina. Marked hyaline degeneration. No metastases.

CASE 3.—BILLROTH, 1869. A male of middle age, with a pulsating tumor of the lower half of one tibia. Amputation. On section, the canal of the lower part of the tibia was filled by the tumor. Microscopically, the growth was very rich in thin-walled blood-vessels, and was composed of epithelial cells. Origin: The blood-vessels of the bone marrow; probably perithelioma.

CASE 4.—ENGELMANN, 1871. A male, forty-eight years old, developed a tumor of the sternum and ribs the size of a man's head. Multiple metastases of lungs and lymph-glands. The tumor was firm, encapsulated, and had cysts containing colloid material.

Microscopically, the tumor was composed of round and elongated alveoli and gland-like columns of cells, with colloid degeneration. Engelmann regarded the marrow cells as the origin of the tumors; probably endothelium of lymphatics.

CASE 5.—JAFFÉ, 1874. Male, aged twenty-four years. A pulsating tumor of the left iliac bone developed to the size of a pear in six months.

Partial extirpation; death.

The left iliac bone was extensively invaded by a tumor mass with an alveolar structure and many small cavities. Near the centre these were the size of a pea and red in color.

At autopsy, numerous metastases were found in the lungs and pleuræ. On microscopical examination, the tumor was very vascular and showed an alveolar structure, some of the spaces resembling acini. There were spaces lined with several rows of cylindrical cells and containing no blood-corpuscles.

Origin.—Jaffé thought the inner layer of the periosteum.

CASE 6.—SUDHOFF, 1875. Female, aged thirty-two years, complained of pain in the joints for three years. There was a tumor of certain of the spinal vertebræ and of the sacrum. Death from pressure-myelitis. At autopsy the seventh dorsal vertebra was swollen, the bodies of the twelfth dorsal and first lumbar vertebræ were softened and invaded with a grayish white marrow-like substance. From the tenth to the twelfth dorsal vertebræ a tumor mass compressed the spinal cord. The second, third, fourth sacral vertebræ, the sternum and left femur were also involved. The femur was the seat of a spontaneous fracture.

In structure the tumors were in some places composed of large cells, round or polygonal in shape, with single nuclei and arranged in large alveoli supported by a stroma of fibrous and elastic tissue. In other places the arrangement was tubular, with cylindrical or flat cells and containing a fine lumen.

The origin of the growth was thought to be from the vascular endothelium.

CASE 7.—SCHWEININGER, 1876. A large centrally situated "adenoid" sarcoma of the humerus (sex and age not given). Microscopically the growth showed a plexiform arrangement and gland-like tubules. The origin was thought to be from the endothelial cells of the blood and lymph vessels and lymph spaces.

CASE 8.—V. LUKOVICZ. Male, aged sixty years. For twenty-one months before coming under observation sciatic pain on the right side. When first seen he had a diffuse thickening of the upper part of the right femur. In a short time there developed a rapidly growing tumor of the upper third of the femur, with spontaneous fracture of the latter. Death occurred eight months after the first occurrence of the sciatic pain.

At autopsy there was found a large mucoid tumor which involved two-thirds of the shaft of the right femur. On section the growth had a spongy appearance and contained a number of cysts containing mucoid material. There was extension to the pelvis and metastases in the pleuræ.

Microscopically the tumor consisted of large and small cyst cavities lined with low cubical or cylindrical cells of the epithelial type. The cavities contained mucus, as did some of the cells. The tumor apparently took its origin from the endothelial cells of the connective-tissue lymph spaces.

CASE 9.—KOLACZEK, 1880. Male, aged eighteen years. A large tumor of the upper part of the left tibia which had developed in five and a half months. The leg was very much enlarged; slight enlargement of the inguinal glands.

Amputation.—The greatest length of the tumor was 22 centimetres and the greatest width 30 centimetres. It consisted of a hard and soft part, the latter containing cysts. The firm portion showed the histological structure of a spindle-cell sarcoma, while the soft portion showed endothelial lined spaces containing no blood-corpuscles.

Origin.—Probably from lymph spaces and vessels.

CASE 10.—ZAHN, 1889. Female, fifty-three years old, had a tumor of the base of the skull with numerous metastases (vertebræ, ribs, and liver). Microscopically the tumor showed an alveolar structure with bands and tubules of epithelial-like cells, some of which showed colloid degeneration.

The tumor was thought to have its origin in the endothelium of the blood capillaries. A second case reported by Zahn (*Beitrage zur Geschwulstelehre, Deutsche Zeitschrift für Chirurgie,* 1885, No. 22), reported as a multiple myeloma, is included in Volkmann's list, but I think that, with the similar tumor of Rustilzky, it should be excluded.

CASE 11.—HILDEBRANDT, 1891. Male, forty-five years of age. In childhood he sustained a fracture involving the right elbow. Nine months before coming under observation he had pain in the right arm; six months before being seen there was swelling of the right arm, and fourteen days before there was a spontaneous fracture. Amputation at the elbow; no recurrence on discharge one month later.

The tumor, which involved the lower end of the arm, was nodular in places, but the joint was intact. There was a fracture of the bone at the seat of the tumor. The latter was the size of a child's head, soft, and on section was red in color, and contained a central cavity, the size of an apple, filled with reddish gray material. The tumor was very vascular. It extended to the periosteum.

Histologically the growth consisted of blood-vessels, usually capillaries, from the sides of which there were cylindrical cells arranged in regular rows, forming tubules. The vessels contained red blood-cells.

Origin.—Stated as the perithelial cells of blood-vessels.

CASE 12.—DRIESSEN, 1893. A male, aged seventy-four years, had pain in the left elbow for two or three years. On admission there was a small tumor of the upper end of the left ulna. The tumor was removed, and there was no recurrence fourteen months later. The tumor was egg-shaped and measured 6 by 4 centimetres, and was firm in consistency. In places it was white, and in others of a dark-brown color.

Histologically the tumer showed both alveolar and tubular arrangements. The cells lining the spaces were epithelial-like, cylindrical, oval, and polygonal in shape. The growth was well supplied with blood-vessels and fibrous tissue. The tumor cells contained fat and glycogen. Driessen thought the tumor had its origin in the endothelium of the lymph spaces of the bone marrow. There was no apparent connection with the blood-vessels.

CASE 13.—SPIEGELBERG, 1894. Female, aged sixty-two years. No history was obtained. At autopsy there was widespread tumor formation in various bones; the tumors varied from a walnut to a fist in size. They evidently had their origin in the bone marrow. Especially large growths sprang from the right os ilii and from the right metatarsal bone. The ribs and sternum were extensively involved. A small metastasis was found in the spleen; the other organs were free from tumors.

Histologically the tumors showed a well-developed fibrous tissue stroma marked in places by the presence of spindle-shaped cells. In this stroma there were large and small alveoli containing cells of the size of ordinary pavement epithelial cells with round, deeply staining nuclei. The cytoplasm stained well with eosin. The cells varied markedly in shape and size; some were the size of ganglion cells. The cells were arranged in rows and cylinders, and between some rows a definite lumen could be made out. Spiegelberg regarded the growth as an endothelioma developed probably from the lymph spaces. Spiegelberg alludes briefly to a second and apparently similar case, without giving, however, either clinical or anatomical details.

CASE 14.—VOLKMANN, 1895. Female, aged seventy years. Two years before admission she noticed a slow growing tumor the size of a walnut on the back of her head. Eighteen months later it began to grow rapidly and was quite soft. On admission there was a soft, elastic, fluctuating, pendent tumor the size of a child's head growing from the occipital region. At one part there was an area of ulceration. On pressure pulsation was felt. At the base one could feel a circular perforation of the skull.

The tumor was extirpated and found to spring from the bone. The dura was normal. Death ten days after the operation. Autopsy. No metastases. The tumor was soft, pale, and marked here and there by reddish areas.

Histologically the tumor presented a groundwork of a spindle-cell tissue, supporting numerous gland-like tubules lined with a single and in some places multiple rows of cylindrical cells which could not be distinguished from cylindrical epithelial cells. These cells had large oval nuclei situated at the base of the cells. Among these high cells there were some cubical and polygonal-shaped cells. The lumina of the tubules were in general round. Some contained colloid or hyaline material. The origin of the tumor was traced to the spindle-shaped cells of the bone marrow, only a portion of which is in relation with the blood capillaries. Volkmann concludes that the cells separated from the vessels to form columns and to develop into gland-like tubules with cylindrical cells.

CASE 15.—MARKWALD, 1895. A male, aged fifty-six years, was taken ill in the spring of 1893 with pains in the back, chest, and joints. By

December, 1893, he was weak, his head rested on his chest, and the abdominal vertebræ were bent backward and to the left side. The deformity increased, and the patient died July 2, 1894. At the autopsy nothing of special interest was found in the internal organs. The head and body were cut in sagittal section in the middle line. The brain and cord were normal. The bones of the skull showed a number of small, reddish-brown, soft, very vascular tumor masses. Similar new growths were present in the bodies of most of the vertebræ, in the ilium, and the long bones of the extremities and the ribs. In the latter the tumors were both periosteal and in the marrow. All the tumors appeared to be of about the same age.

Microscopically, the tumors were composed of a connective-tissue stroma rich in capillaries, with cell masses arranged in rows suggestive of carcinoma. The cells had large, round nuclei surrounded with a considerable amount of protoplasm. The cells often formed long rows. Many of the spaces contained blood. The tumors sprang from the endothelium of the small capillaries and were classed as an intravascular endothelioma. The tumor tissue was not circumscribed, but tended to spread.

Case 16.—Gaymard, 1898. Female, aged nine years. She always had had good health until some months before coming under observation. Five months later she fell from a carriage, striking her head. There was a fracture of the left hip at the trochanter, where a tumor mass was felt. Fifteen days after the fall a small tumor was discovered at the junction of the right frontal and parietal bones. This tumor was soft, and on excision had the appearance of human muscle. Diagnosis. Angiosarcoma of the upper end of the left femur with metastases in the skull. Operation. Excision of the tumor of the skull.

Histologically the tumor was composed of a net-work of vascular tissue, with a delicate connective-tissue framework limiting large alveoli, and between this framework and the vascular spaces containing red blood-corpuscles there were from five to ten rows of round or polygonal cells; thus, a vascular lumen, stratified rows of cells, then supporting connective tissue. Gaymard regarded the cells as endothelial in origin.

Case 17.—Ritter. A female, aged fifty-one years, had pain in the right leg for six months. Three months later there was a swelling of the right leg and foot. Examination showed a fluctuating, pulsating tumor connected with the lower end of the tibia. Operation at the knee-joint. The tumor was spindle in shape; it began 3 centimetres above the ankle-joint, and was 8 centimetres long and 19 centimetres in circumference. Just above the tumor there was an old fracture of the tibia. The periosteum was thickened over the tumor, which in places penetrated the former. On section the tumor was soft and juicy, and of a dark brownish red color. No bone was found in the tumor. No metastases were made out. The tumor was composed of a structure of rather large cells arranged in places in long single rows, in places in solid nests or cords of cells, and in other places, still, in larger and smaller spaces or cavities. In the last case the cells were large, oval, round, or pointed, and rested against capillary vessels which often contained red blood-cells. There was no membrana propria. The large spaces which contained blood were round, oval, or tubular in shape, and often communicated. Their lining cells rested directly upon capillary walls. The cells contained large fat drops, and some a material staining brown with iodine. The protoplasm of the cells was granular. The nuclei were large and stained deeply.

Origin.—Stated as the perithelial cells.

Case 18.—Berger, 1900. Female, fifty-eight years old, was admitted to the hospital in November, 1898, with a pulsating tumor and spontaneous fracture of the upper portion of the left humerus. In the previous June she had transient pains in the lower extremities and pain and loss of use of the left arm. On admission there was a pulsating tumor, the size of a mandarin, in the inferior deltoid region. The neighboring glands were not enlarged, the heart and lungs were negative.

Diagnosis.—Pulsating angiosarcoma of the humerus. Amputation. About two weeks later there appeared a swelling of the left side of the face, which later involved the orbital and frontal regions. At the same time the pains in the lower limbs returned. Some months later a tumor developed in the upper part of the left thigh. In June there was a spontaneous fracture of the superior portion of the left femur. There was pain in the trunk, and on one occasion blood in the urine. The tumors increased in size and the patient was bedridden. The upper part of the humerus, except the head and surgical neck, was destroyed by the growth, which was limited by a capsule which was continuous with the periosteum and separated the tumor from the surrounding soft parts. The tumor was continuous with the medullary tissue of the bone, and was soft, friable, spongy, and of a red-wine color. It contained spaces filled with blood and dark clots.

On histological examination by Dr. Bebançon the tumor was found to be surrounded by a connective-tissue capsule rich in blood capillaries. The tumor proper was composed of alveoli with thin connective-tissue stroma supporting cells of varying size. The thin alveolar walls consisted mainly of blood capillaries from 9 to 10 microns wide, which anastomosed with the vessels of neighboring alveoli, which were sometimes cylindrical, sometimes polygonal, or even round when they were about a lumen. The cells were in the main rather large,—15 to 20 microns in diameter. The cells had clear cytoplasm which stained with neither acid nor basic stains. They contained a single central vesicular nucleus with little chromatin and a large nucleolus. No karyokenesis was observed.

Origin.—Endothelium or perithelium.

There was a marked likeness to the tumor reported by Gaymard.

Case 19.—Sternberg, 1901. Female, aged sixty-six years, had pain in the back and knees for fourteen days. She was anæmic and presented the clinical picture of pernicious anæmia, but no blood examination was made. She died two days after admission.

Autopsy.—The body was poorly nourished; no deformities of the skeleton. The lungs, pleuræ, and heart were negative. The liver showed a number of small nodules. The gall-bladder and bile ducts were negative, as were all the other organs except certain bones. The right femur and humerus, on section, showed scattered, soft, grayish white nodules. The sternum, ribs, vertebræ, sacrum, and cranial bones showed similar nodules.

Sections of the tumors of the marrow of the various bones showed large round, clear, swollen cells with peripherally placed, half-moon or sickle-shaped well staining nuclei. The cell body had a finely granular border, while the inner part of the cell contained one or more vesicles or spaces (fat spaces). In some cells the cytoplasm was transformed into a large vesicle containing finely granular material. The cells were supported by a net-work of fine capillaries forming an alveolar arrangement. Giant cells were found in some places. The tumor cells contained no glycogen. No micro-organisms were found.

PERSONALLY OBSERVED CASES.

CASE 20. (Case I, HOWARD and CRILE.)—*Primary Perithelioma of the Left Humerus ending in Spontaneous Fracture; Non-union of the Fracture. Metastasis on the Tip of the Nose. Amputation of the Humerus and Tip of the Nose; Death on the third day.*

Clinical History (Dr. Crile). *Personal History.*—The patient was a well-built man, sixty-five years of age, and of a sturdy family without any history of malignant disease. He had always been active in business, and in his later years carried heavy responsibilities. There was no history of serious illness except several attacks of appendicitis.

Two years before the fracture of his humerus he fell down an elevator shaft for two stories without serious injury. He had been accustomed to drive a spirited trotting horse, even up to the time of the spontaneous fracture.

Present Illness.—For about two years prior to the fracture he suffered considerable pain in the humerus near the point of the fracture. The pain was not influenced by the weather, exercise, or by pressure, neither by treatment. While tossing a tennis ball preparatory to serving, his arm suddenly snapped and fell helplessly by his side. A temporary dressing was applied by Dr. N. C. Varian, after which he was under the care of his physician, Dr. C. B. Humiston. The fracture was transverse and was easily kept in place. There was nothing unusual in its clinical course excepting the tardy repair. On the second and third weeks there was a fairly good callus, but later this diminished and almost disappeared. At this time I became associated with Dr. Humiston. The tumor of the nose was such as to give the end of that organ the appearance of a greatly exaggerated tippler's nose,—red, tuberous, elongated, and slightly turned up.

On close inspection the numerous blood-vessels increased in density towards the tip, and faded out upward and laterally. There was neither pain nor tenderness. On palpation a distinct pulsation could be made out.

A diagnosis of angiosarcoma was made; a section, under local anæsthesia, was removed and submitted to Dr. W. T. Howard, Jr., who returned the diagnosis of perithelioma.

The fracture was believed to be due to a similar process in the humerus. At the end of eight weeks the humerus at the point of fracture showed pulsation.

Dr. Humiston, assisted by Dr. Hain, Dr. Fitzgerald, and myself, performed the operations.

The patient bore the operations well, but developed some obscure pulmonary symptoms on the third day and died rather suddenly. No autopsy was made.

The arm and the nose were submitted to Dr. W. T. Howard, Jr., for pathological investigation.

Pathological Report (Dr. Howard).

(*a*) Small portion of tissue removed from the tip of the nose by Dr. Crile for microscopical examination. The specimen consisted of a small piece of skin and underlying tissue.

On microscopical examination the epidermis was found unbroken, somewhat thinner than normal, but otherwise unchanged. Beneath the skin and entirely unconnected with the epidermis there were a number of large capillaries and blood sinuses of varying size, surrounded by from one to three or four rows of large oval or polygonal cells with faintly staining vesicular nuclei, which usually contained nucleoli. Many of the nuclei showed mitoses. The outlines of most of the cells were very distinct; the cytoplasm was often vacuolar and sometimes finely granular. In many cells it was very obscure. The new growth was not encapsulated and extensively invaded the surrounding tissue. A diagnosis of endothelial hæmangiosarcoma was made, and immediate operation for the growths of both the nose and the humerus advised.

(*b*) On November 21, the tip of the nose and the left upper extremity of this patient were received at the laboratory.

Nose.—The specimen consisted of the end of the nose, including both alæ nasi, and measured 3 by 3.5 centimetres. At the tip there was an elevated tumor nearly round in outline and projecting from 8 to 12 millimetres above the surrounding skin. At one portion there was a small area of ulceration, and at another a globular protuberance .5 centimetre in diameter.

On section the tumor was 1.5 centimetres wide and 8 to 10 millimetres in depth, and of a grayish pink color. Its margins were irregular. At one point the tumor approached but did not invade the cartilage of the nose. The skin and underlying tissues were otherwise unaffected.

Portions of tissue were hardened in Orth's and Zenker's fluids and in alcohol, and stained with hæmatoxylon and eosin, eosin and methylene blue, and Weigert's elastic tissue stain. Sections through the whole growth showed that it was covered with unbroken skin, except at one point where the epidermis was entirely lost; the underlying tissue was infiltrated with red blood-cells, leucocytes, and plasma cells. At this point the tumor was from 1 to 2 millimetres beneath the surface, from which it was separated from the necrotic and infiltrated dermis by a thick layer of fibrous tissue. The new growth was in no way connected with the epidermis or the glands of the skin. It was surrounded by a rather dense fibrous tissue which it infiltrated on all sides. The tumor was separated into a number of well defined but irregularly oval areas by dense, white fibrous tissue bands, which were poor in nuclei and blood-vessels. The new growth was composed of a large number of capillary and venous spaces containing red corpuscles and lined by from one to four or five or more layers of large, round, oval, or polygonal cells with faintly staining nuclei. Here and there were larger and smaller spaces without visible lumina filled with large, flat cells like endothelial plates. Large blood sinuses lined with a single or double row of cells were numerous. No elastic tissue was found in the tumor.

Arm.—The specimen consisted of the left upper extremity. The forearm, hand, and fingers were normal. The arm measured 54 centimetres in length. In its middle third there was a tumor involving the whole thickness of the humerus, the periosteum, and a portion of the muscles for a distance of 10 centimetres.

The skin was normal. The tumor was 15 centimetres in its greatest diameter. The muscles were irregularly invaded, the periosteum could not be made out, and a few spicules of bone represented the remains of the shaft of the humerus throughout the extent of the tumor. The marrow cavity, as well as the bone, periosteum, and muscles, was transformed into a homogeneous, pale, grayish-red tissue of a soft spongy consistency. A small amount of blood escaped on section. There were no cysts. The edges of the bone at the upper and lower borders of the growth were rough and irregular, but firm. The new growth invaded the marrow cavity for some distance above and below the main portion of the tumor. The head of the humerus was normal. The elbow-joint contained a small amount of clear fluid. Cultures from the tumor remained sterile.

Small pieces were cut from the various portions of the new growth, and from the humerus and its bone marrow and hardened in Zenker's and in Orth's fluids. Sections were stained with hæmatoxylon and eosin, methylene blue and eosin, with and without Weigert's elastic tissue stain, and with Mallory's connective-tissue stain.

The new growth was composed of a groundwork or supporting tissue, of sometimes thin and sometimes thick branching bands of rather dense, white fibrous tissue. In some places, especially where the growth was invading neighboring tissue, the supporting tissue had a hyaline, homogeneous appearance and contained relatively few elongated nuclei. No elastic fibres were found in this tissue.

The essential structures in the new growth were, however, numerous capillaries and sinuses of varying size containing a varying number of red blood-cells. These spaces were lined with from one to five rows of round, oval, or polygonal cells, with faintly staining and often vesicular nuclei, which often contained nucleoli. Nuclear figures were plentiful.

The cell walls were very prominent, while the cytoplasm was often indistinct and did not take the eosin stain. It was commonly finely granular and often vacuolar. The cells were often arranged in regular rows like glandular epithelium, and in this case were commonly columnar in shape, with their nuclei situated at the end of the cell furthest from the lumen. The tumor cells varied from 8 to 15 microns in diameter.

The blood spaces varied greatly in width, some being filled by a single red blood-cell on edge, while others were from 20 to 30 or even 200 microns in diameter. In some places the growth was alveolar in structure, there being no lumina, but the spaces completely filled with cells of the endothelial type. There was rather free communication between the blood spaces, which varied from long tubules to round spaces. The tubular structures ran in various directions. On cross-section they closely resembled gland ducts lined with cubical or columnar epithelium. In many places, especially where several spaces opened into each other, typical papillary processes were seen. They were composed of a thin layer of supporting fibrous tissue, covered with a single layer of cells.

The absence of a membrana propria was striking, the cells being in direct relation with capillary walls or with the supporting connective-tissue bands. A capillary could usually be traced between the neighboring or adjacent tubules or alveoli, the cells of which abutted the vessel. The spread of the new growth could be readily traced from the cells lining the blood spaces. In many places at the margins of the growth single and double rows of these cells could be traced making their way far out into the neighboring tissue. All gradations could be made out between these cells and the tumor cells. While relations of the new growth to the capillaries were intimate, positive proof of the origin of the tumor cells from the vascular endothelium was not obtained. The new growth could not be traced to the lymphatic structures, either. The tumor is therefore in all probability to be classed among the so-called peritheliomata whose histogenesis will be discussed later. As the growth advanced, the surrounding tissue, whether bone marrow, bone, periosteum, muscle, or connective tissue atrophied and was infiltrated. The head of the humerus was not invaded. No newly formed elastic tissue was found in the tumor.

A small amount of blood pigment was present in the tumors of both nose and bone. Tests for glycogen were negative.

These growths were identical in structure. From the clinical history and the study of the tumors there is little doubt but that the nasal tumor was a metastasis for that of the humerus. It is much to be regretted that an autopsy was not granted.

CASE 21. (Case II, HOWARD and CRILE.)—*Primary Peri-*

theliomata of the Left Humerus with Metastases of the Left Temporal Bone, the Pleuræ, Lungs, and Liver. E. S.; male, aged thirty-one years; white; single; a patient at the Cleveland City Hospital, service of Dr. C. F. Hoover.

In January, 1899, he had a spontaneous fracture of the middle third of the left humerus. The bone apparently knit, but nine weeks later a second fracture occurred at the same place. Shortly after the first fracture the patient noticed a small nodule over the right temporal bone. He died of exhaustion, August 2, 1899, about seven months after the first fracture of the humerus.

Autopsy.—The body was markedly emaciated. The middle third of the left humerus was the seat of a large, soft, grayish red tumor. Occupying the space between the left orbit and the left ear there was a large tumor the size of an orange. The latter growth was continuous with the temporal bone, which was soft and friable. This tumor was soft, grayish-red in color, and quite vascular. The surface of the body and the other bones as far as could be determined were free from metastases. Metastatic nodules from 2 to 10 millimetres in diameter occurred in both pleuræ, both surfaces of the diaphragm and in both lungs, and on the superior surface of the liver. The bronchial glands and mediastinal tissue were extensively invaded. The other organs were without present interest.

Histological examination of bone tumor. Sections made from various parts showed very much the same appearances. The bone tissue was largely replaced by a new growth composed of a fibrous tissue stroma which, in general, was quite thin, often consisting mainly, and sometimes entirely, of single narrow blood capillaries, forming alveolar spaces, which were filled with cells of varying shape and size. In most places the cells lay in direct relation with the capillary walls, which to a great degree formed the boundaries of the alveolar spaces. The latter were round or oval in outline and from a few to 200 or 300 microns in diameter. The cells were from 8 to 16 microns in diameter, and were round, oval, or polygonal in shape. Often they formed large flat plates like endothelial cells. They were often placed in long rows, but only occasionally could a lumin be made out. No columnar cells were found. Many giant cells were present in some places. The cells had large, oval, vesicular nuclei, each with a nucleolus. The cytoplasm was finely granular and stained well with eosin. The cells were intimately connected with the capillaries. The bone disappeared before the advancing growth. This tumor in structure is a typical example of the so-called perithelioma of Hildebrandt.

The metastases of the pleuræ, lungs, and liver showed a structure identical with that of the original tumor.

Diagnosis.—Primary so-called perithelioma of the left humerus with metastases of the left temporal bone, the pleuræ, lungs, and liver.

CASE 22. (Case III, HOWARD and CRILE.)—*Primary Endothelioma springing from the Lymph Spaces and Channels of the Lumbar Vertebræ, Clavicle, and Ribs, with extensive Metastases. Chronic Cholecystitis with Gall-stones and thickening of the Gall-bladder.* I. M.; male; white; aged forty-five years, entered the Lakeside Hospital, service of Dr. Edward F. Cushing, June 16, 1901, complaining of pain in the left side and back. His family history was negative. He denied syphilis and gonorrhœa. He had always been well until seven weeks before admission, when he was taken ill with pain in the abdomen, left side, and back. His bowels were constipated. The pain was worse at night and ran up and down the back. He was treated by his physician for lumbago. He said he passed less urine than formerly. The patient recalled having had a fall on January 1, 1901, but says he felt perfectly well afterwards until the present illness.

On admission, examination of the heart, lungs, liver, and abdomen were negative. There was no disturbance of the sense of temperature. The spinous processes of the third and fourth lumbar vertebræ were more prominent than normal, and pressure on the lumbar muscles caused great pain. Turning in bed and walking were accomplished with difficulty. In walking, the legs were dragged along with a shuffling gait. In stooping, the back was held rigid. When the head was tapped, sharp pain was felt in the lumbar region.

The urine was clear, of an amber color, sp. gr. 1030, acid, free from sugar. No albumen (albumose not recorded). No casts, a few leucocytes. The patient ate little and steadily declined. On July 5 a small subcutaneous nodule was noticed on the right side just below the ribs in the posterior axillary line. Later, a similar nodule appeared on the opposite side.

On July 20, a painful swelling of the sternal end of the left clavicle was noticed. Blood examination, July 17, showed leucocytes 10,000 per cubic millimetre; hæmoglobin, 89 per cent. July 21, the leucocytes were 22,000 per cubic millimetre. The patient died July 29, 1901, after having been comatose for three days.

Autopsy two hours after death.

Abstract of the autopsy protocol. The body was 165 centimetres long and very much emaciated. On the left sternoclavicular articulation there was a well-marked tumor mass. The joint was movable and crepitant. Small subcutaneous nodules were present on the chest, abdomen, back, and left buttock. On section they were firm, translucent, and glistening. The sternum, costal cartilages, and mediastinum were negative. The tumor of the left clavicle was firm and translucent and grayish-white in appearance. Similar masses were present in the third and fourth ribs of the right side.

The bodies of the third and fourth lumbar vertebræ were softened and cut with comparative ease; the bone tissue was almost entirely replaced by a grayish-white translucent tissue. The body of the second lumbar vertebræ contained an oval nodule 2 by 12 centimetres in diameter, and of a similar appearance. The bodies of the third and fourth lumbar vertebræ were flattened, the periosteum thickened, and in places extensively involved in the tumor tissue. This was especially well marked on the posterior surface of the bones where the tissue was soft and readily compressed. The spinous and transverse processes of the third and fourth lumbar vertebræ were thickened and extensively invaded with tumor tissue. A mass of tumor tissue, 2 by 1 by 1.5 centimetres, projected from the spinous process of the third lumbar vertebra into the spinal canal and compressed the cauda equina. The dura was not affected, but the canal contained a large amount of clear fluid. A similar but smaller mass was found opposite the fourth dorsal vertebra; the cord was not compressed at this point. The left psoas muscle, near the bodies of the second and third lumbar vertebræ, was the seat of an irregular tumor mass 3 by 2.5 centimetres in diameter. On section this mass was found to be directly continuous and identical in structure with the new growth of the vertebræ. As far as could be determined, no other bones were affected. Examination of the brain was not allowed.

The vascular system showed nothing abnormal. A few small nodular masses were found in both lungs. The peritoneal cavity contained 2500 cubic centimetres of greenish yellow fluid. The peritoneum over the intestines was studded with numerous small pale elevated nodules. The liver weighed 1650 grammes. The surface was covered with numerous pale elevated areas from 0.25 to 0.5 centimetre in diameter. The ligaments were thickened and contained similar nodules. On the extreme right border of the liver there was a firm nodule 5 x 3 centimetres. On section the organ was bile stained, and was studded with numerous brown or yellowish, firm, small areas which were sharply defined from the liver tissue. The lobules were visible. The bile ducts were dilated.

The gall-bladder was quite small and its walls very much thickened. On section the walls were dense and firm, the cavity much reduced in size, and contained fifty-five yellowish-brown stones. The mucosa was red, but showed no special thickening and no evidence of tumor formation. The hepatic duct was dilated, the cystic and common ducts normal.

The lumbar, mesenteric, gastrohepatic, peripancreatic, and bronchial lymph-glands were large, firm, and translucent on section. They were extensively invaded by metastatic growths.

The other organs are without present interest.

The tumor was evidently primary in the lumbar vertebræ (possibly the ribs and clavicle), whence metastases occurred by extension into the surrounding tissue (psoas muscle), thence to the lumbar and mesenteric and other lymph-glands, the peritoneum, liver, and lungs.

The macroscopical resemblance of the tumors to carcinoma was striking.

Histological Examination.—Sections of the bones. Bodies of lumbar vertebræ. Sections from the centre of the growth show dense, fibrous tissue stroma rather scantily supplied with blood capillaries containing a variable number of spaces filled with large cells. The cells in places formed long rows, sometimes single, but usually double or even treble. In other places there were round or oval alveolar spaces filled with cells. No lumina were to be seen. Between the cells, both in rows and in alveoli and the stroma in most places, a definite row of thin flat cells in all respects like the endothelial plates of lymph spaces and vessels could be seen. In a number of instances the development of these lining cells into the tumor could be traced; this occurred by the swelling of both nuclei and cytoplasm, with the transformation of the thin plates into large cells, with swollen vesicular nuclei. The tumor cells varied very much in size, from that of a polymorphonuclear leucocyte to huge multinuclear giant cells. They were usually polygonal, but sometimes round, often oval, and in many cases, especially when lying in single rows in narrow lymph spaces, very much elongated. In general they were large cells. The cytoplasm was smooth or finely granular, and stained faintly with eosin. The nuclei were large and vesicular, with well-marked rims, and contained one or more nucleoli. In many of the large cells from three to six nuclei could be made out. Nuclear figures were numerous. Nuclear and cell inclusions were not uncommon. In sections at the advancing border of the growth in bone the origin of the tumor from the endothelium of the lymph spaces and vessels, especially the perivascular lymph spaces, was evident. Here in the soft bone marrow large alveoli of tumor cells were numerous. Following the proliferation of the endothelial cells of the lymph spaces and lymph vessels there was a growth of dense fibrous tissue. The advancing border of the growth was much more cellular and softer than the older portions. With the growth of the fibrous tissue, stroma resorption of bone occurred.

In sections made through the fourth lumbar vertebræ and its periosteum and the surrounding tissue, the spreading of the tumor tissue to the latter could be clearly seen. Sections made from the new growths of the clavicle and ribs showed the same structure described in the vertebræ, except that a better opportunity was given for the study of the origin and spread of the tumor tissue, which could be readily traced from the endothelium of the lymph spaces and lymph vessels, especially from the perivascular lymph spaces.

Lymph-glands, mesenteric and bronchial. In the sections studied, the lymphoid tissue was almost entirely replaced by a new growth made up of large and small alveoli filled with large cells with large vesicular nuclei. Nuclear figures were numerous. No tubular formations were found.

Liver.—Scattered throughout the liver there were a large number of small metastases situated near the portal systems. They showed the same structure as elsewhere, but the tumor cells were crowded together more closely than in other organs. The liver-cells in many places were shrunken, compressed, and contained a large amount of pigment. In the portal systems which were not involved in the tumor metastases, the bile ducts and the portal connective tissue contained a considerable amount of bile pigment.

Sections of the gall-bladder showed desquamation of the lining epithelium, with dilatation of many of the glands and desquamation of the glandular epithelium. In many places the glands were absent. The wall of the gall-bladder much thickened by the presence of a dense fibrous tissue with scattered areas of round-cell infiltration. No tumor was to be made out, though numerous sections from various parts were examined.

Lungs.—In sections of the lungs the metastases were found mostly above the small bronchi, involving the pulmonary vessels, the peribronchial tissue, and often groups of tumor cells were found in the alveoli. In some places subpleural metastases were found. The pulmonary metastases showed the same structure as the original tumor and the other metastases.

Sections of the omentum showed extensive metastases always along the lymph channels and spaces.

Heart.—Sections of the heart muscle (left ventricle) showed a small metastasis. The spleen and pancreas were negative. The kidneys were the seat of chronic interstitial nephritis.

A study of the gross and microscopical lesions showed clearly (1) That the lumbar vertebræ were the primary seat of the new growth; (2) that the tumor spread first through the vertebræ to the surrounding tissue, thence by the lymphatics to the lumbar and mesenteric lymph-glands, the omentum, the peritoneum, and the hepatic lymph-glands; thence to the liver, lungs, heart, clavicle, and ribs. (3) The new growth was an endothelioma springing from the endothelial cells of the lymph spaces and vessels of the lumbar vertebræ.

Anatomical Diagnosis.—Primary endothelioma of the third and fourth lumbar vertebræ, with metastases in the perivertebral tissue, the left psoas muscle, the lumbar, mesenteric, and bronchial lymph-glands, the omentum, peritoneum, liver, lungs, heart, clavicle, ribs, and sternum. Slight fibroid tuberculosis of the lungs. Chronic cholecystitis, with gall-stones, and thickening of the gall-bladder. Cultures from the lungs showed Staphylococcus pyogenes aureus and Bacillus mucosus capsularis,—other organs negative.

CASE 23. (Case IV, HOWARD and CRILE.)—*Primary Lymph Endothelioma of the Left Femur, with Metastasis in the Inguinal Lymph-Glands. Autopsy not obtained.*—Female, aged eleven years. Consulted Dr. Costello, July 15, 1901, complaining of pain in the left femur just above the knee-joint. There was no history of tumors in her family. The father and mother and several brothers and sisters were well. No history of tuberculosis or syphilis was obtainable. The child had had both measles and scarlatina. The child walked into Dr. Costello's office with a slight limp. There was no increase of pain on walking, bending the knee, or on pressure. On percussion there was deep-seated pain. There was slight symmetrical swelling of the left thigh just above the knee. Pulsation was not noted. On questioning the child, she stated that about June 1 she had a fall while playing in the school-yard. Examination by Dr. Costello showed a small abrasion of the skin below the point of swelling. There was no noticeable enlargement of the inguinal or other lymph-glands. The temperature was 99° F.; the pulse normal. *Diagnosis.*—Osteomyelitis.

Operation, July 17, by Drs. Gallagher and Costello. A longitudinal incision was made through the skin and soft parts, about five inches in length, on the outer surface of the left femur, at the point of swelling, and extending through the periosteum. The subcutaneous tissue was entirely normal in appearance. The periosteum appeared somewhat thickened, but not noticeably congested. The bone was firm but appeared thickened. About a teaspoonful of puriform (?) material was obtained from the marrow cavity. The wound was packed with gauze. There was no discharge of pus. About two or three weeks after the operation there was a slight uniform swelling of the lower end of the thigh. Very exuberant granulations formed in and about the sinus which persisted six weeks after the incision. The thigh became progressively larger, until by November it was the size of a bucket, the swelling being uniformly round in outline and extending from the knee to near the hip-joint. The inguinal glands became swollen and tender, but no other glands were involved, and no other tumors were apparent. There was no pulsation of the tumor. Springing from the seat of the incision there developed a globular tumor mass the size of a man's head and uncovered by skin over a considerable area. Pain was marked. There was no fracture. She was seen by Dr. Crile in consultation in November.

Sections made from the piece of tissue excised by Dr. Crile showed a dense fibrous tissue stroma supporting occasional strands and alveoli of cells. Many alveoli were large and contained thin elongated cells. Some of the cellular strands were quite long.

The cells were large, of the endothelial type, and had rather large nuclei. Many of the cell collections were evidently in lymph spaces, from the lining cells of which their origin could be readily traced. The alveoli were evidently formed by the multiplication of the endothelial cells of these spaces. The blood-vessels took no part in the new growth.

GENERAL PATHOLOGY.

(*a*) Analysis of the 23 known cases shows as follows:

Seat.—Long bones were involved in 19 cases (humerus 7, tibia 3, femur 8, ulna 1); all the long bones, 1, flat and spongy bones in 15 cases (most of skull bones 1, base of skull 2, temporal and frontal bones 2, iliac bone 2, sternum 4, vertebræ 4).

Size.—The tumors were large in 11 cases, of moderate size in 7, and small in 5 cases.

Thirteen were said to be soft, 5 hard, and 5 elastic.

On section, the prevailing color was red or gray red.

Cysts of varying size, usually containing bloody fluid, were found in 8 cases. Of the 16 cases involving the long bones, spontaneous fracture occurred in 7.

In most cases the growth started in the central portion of the affected bone, spread along the marrow cavity, through the bone, and in several cases into the surrounding tissues.

The tumors were quite vascular, and several of the older cases were mistaken for bone aneurisms; seven were said to pulsate.

Metastases occurred in over one-half the cases (14).

In 8 cases the tumors were single and without apparent metastases.

In the 13 cases in which multiple tumors are known to have been present, in only 4 were the bone tumors single. In these 4 cases (Engelmann, Jaffé, von Lukovicz, our Case I), the lungs and pleuræ showed metastases in 3, the primary growths being in the sternum and ribs, left os ilium, and left femur each in 1 case; in the fourth case a primary tumor of the left humerus gave rise to a secondary growth on the nose.

In the remaining cases there were multiple growths in several bones, with metastases in some of the internal organs in 4.

A synopsis of these 9 cases shows as follows: Sudhoff's case, multiple tumors of the dorsal, lumbar, and sacral vertebræ, sternum, and left femur; Spiegelberg's case, right os ilium, a metatarsal bone, sternum and ribs; Marchwald's case, skull, most of the vertebræ, ossa ilia, ribs, and long bones of the extremities; Gaymard's case, left femur and skull; Berger's case, left humerus and femur and the skull (frontal bone); Sternberg's case, right humerus and femur, the sternum, ribs, and several vertebræ; Zahn's case, skull, vertebræ, and ribs; our second case, left humerus and the skull (left temporal bone); our third case, the lumbar vertebræ, clavicle, and ribs. Certain bones were affected with great frequency, the bones of the skull, the vertebræ, the sternum, the ribs, and the femur being the ones most often involved.

Certain combinations of bones stand out prominently; for instance, the skull, the vertebræ, and the ribs, and sometimes the sternum being affected together. The humerus and the femur were simultaneously affected in two cases. In some of these cases it is pointed out in the clinical histories that the tumors apparently involved certain bones after others, but in some instances the tumors of the various bones appeared about the same time and were of apparently the same age. For some cases, at least, it seems not improbable that the tumors started in several bones at the same time, that is, that a number of independent malignant tumors of the same structure originated simultaneously in different bones. Opposed to this view are the fact that malignant tumors rarely originate in multiple foci and the probability that the bone tissue offered a more suitable soil for the growth of wandering tumor cells than certain other organs to which the cells were also carried. In two of these cases the visceral metastases were inconspicuous, while in the remaining two cases they were wide-spread.

The other five cases of multiple wide-spread tumors of bones, like the myelomata, failed to show visceral metastases and the presence of tumors except in bone. Eleven cases are known to have died; in all but one of these an autopsy was obtained. The growth was rapid in nine cases. The growth of the tumors, when small and not involving the viscera, was associated in many cases with prostration and the usual symptoms of emaciation and cachexia. No special blood changes have been noted. Albumosuria was not mentioned in the histories of any of the cases, and was probably not looked for.

Histology.—The histological descriptions of the earlier cases are not very full, but a conformity to two general types is clear; (*a*) vascular tumors with alveoli filled with cells of various types, and (*b*) gland-like structures lined with single, double, or multiple rows of round, oval, polygonal, or even columnar cells of the epithelial type. In some tumors there were both alveolar and tubular structures. Giant cells may be present in both varieties. In both types the relation between the tumor cells and the blood capillaries is usually intimate and conspicuous. In many cases the tumor cells lie against the capillaries, which course between rows of the former. The blood capillaries may contain much or little blood; often they are compressed by the tumor cells. The alveolar walls are in many instances composed entirely of capillaries, while in others the tumor cells are supported by an abundant fibrous tissue stroma. The latter was especially well marked in our Case 3. The gland-like structures—tubular endo- and perithelioma—often form long tubules, and may contain blood. In some tumors the fibrous tissue was scanty, while in others it was plentiful and rich in nuclei and spindle-shaped cells. As far as is known, it is composed of white fibrous tissue. The tumor cells are prone to degeneration, and there are instances of fatty, colloid, hyaline, and myxomatous change. Ritter and Driessen demonstrated glycogen in the tumor cells in their cases. The iodine test for glycogen was negative in our Case 1.

Many of the tumors in bone were not sharply marked off from the marrow tissue. The histological structure is entirely unlike that of myeloma, from which it is readily distinguished. The cells and their arrangement, however, differ rather widely, and this is readily understood when their diverse points of origin are considered.

(*c*) *Histogenesis.*—From analysis of the cases available at the date of his article, Volkmann concluded that these tumors had their origin as follows:

From the endothelium of the lymph sinuses, 4 cases (Lücke, Driessen, Engelmann, and von Lukovicz); from the endothelium of blood capillaries and the perithelial cells, 6 cases (Kocher, Kolaczek, Hildebrandt, Zahn, Jaffé, and Billroth); from the endothelium of lymph channels and blood capillaries, 2 cases (Schweininger and Volkmann); unclassified, 1 case (Sudhoff).

While we do not believe that it is possible to accurately classify these cases according to their histogenesis, a careful study of each leads us to think the following is approximately correct, and as near the truth as it is now possible to arrive. From the perithelial cells of Waldeyer, or the endothelium of perivascular lymphatics, 12 cases (Lücke, Kocher, Billroth, Jaffé, Hildebrandt, Gaymard, Ritter, Berger, Sternberg, and Howard and Crile, Cases I, II, and V); from the endothelium of blood capillaries, 2 cases (Zahn and Markwald); from the endothelium of the ordinary lymph vessels and lymph spaces, 7 cases (Engelmann, Kolaczek, von Lukovicz, Driessen, Spiegelberg, Volkmann, Howard and Crile, Cases III and IV); from the endothelial lining either of the blood capillaries or the lymph vessels, two cases (Sudhoff and Schweininger). If the above is correct, one-half of these tumors are perithelial in origin, while the other half are derived from either the blood or the ordinary lymph-vessel endothelium. The term perithelioma was first applied to certain of these tumors by Hildebrandt. That the tumors in question arise from the perithelial cells of Waldeyer, cells found in relation with the small blood-vessels of certain organs, notably the testis, is by no means proven. As Driessen points out, these cells have not been demonstrated about the blood-vessels of either bone or periosteum. Morphologically, the cells of these tumors are of the endothelial type, and like endothelial cells they lack apparently the property of secreting intercellular substance. Hence it is fair to conclude that they are not of the ordinary connective-tissue type. This being so, it is evident that the tumors classed as peritheliomata must take their origin from either the endothelium of blood capillaries or from the endothelium of the perivascular lymph spaces.

That tumors of the same structure as the so-called bone peritheliomata may arise from the endothelium of blood capillaries, we have had recent evidence in an endothelioma of the breast removed by Dr. Crile, in which there were both closely filled alveoli and tubular structures often containing blood and corresponding exactly with the structure of the tumors of our Cases 1 and 2, which would be classed among the peritheliomata by Hildebrandt and others. In this breast tumor some of the blood capillaries were more or less completely filled with proliferated endothelial cells. In other places the mode of development of the tubular structures could be directly traced from proliferated blood capillary endothelium, the newly formed cells protruding from the capillaries, and forming short or long rows in the surrounding, but otherwise unchanged, connective tissue. The perivascular lymph spaces played no apparent part in the process. The presence of blood in the spaces of the so-called peritheliomata does not prove that these tumors spring from the blood-vessel endothelium, for its presence is readily explained by hæmorrhage, large areas of which are not uncommon; contrariwise, the absence of blood in the spaces cannot be taken as an argument against the blood-vessel endothelium as the origin of certain of these growths.

We are inclined to agree with the opinion of Driessen, Perth, Hildebrandt, and others that the so-called perithelium is in reality the endothelium of the perivascular lymph spaces.

We have not been able to make out in sections of bone marrow any cells which could be classed as the perithelial cells of Waldeyer. In the bone marrow the blood capillaries show no such cells, and are not accompanied by perivascular lymph spaces, which can, however, be made out about the small arteries and veins. Hence we would include among the so-called bone peritheliomata those tumors springing from these cells, as distinguished from the lymph endotheliomata derived from the endothelium of the ordinary lymph spaces and lymph vessels, *i.e.*, those not immediately about the blood-vessels. Judged by the study of our own material, derived from tumors of bone and other organs, it is not possible in most cases to decide whether a given tumor springs from blood-vessel endothelium or perivascular lymph space endothelium (perithelia).

Apparently, there may develop from the endothelium of either of these two places growths of identical structure; that is, the endothelium of either situation may give rise to endothelial cell growths composed of either completely filled alveoli or of tubular spaces (with or without blood-cells in the latter) in which both alveoli and tubular spaces are separated and supported by blood capillaries in direct relation with the tumor cells. The chief difficulty in diagnosis here is due to the fact that growths developing from blood capillary endothelium may form alveoli by proliferation inside the vascular lumen, the alveolar boundaries being furnished by previously existing or newly formed capillaries, or the proliferating endothelial cells may break through the blood capillaries and form either tubular or alveoli structures. Unfortunately, these tumors are not presented for examination in their earliest stages, and one cannot say whether a growing portion of the tumor is derived from the cells of the vessels or spaces in which proliferation is taking place, or the proliferating cells are transported tumor cells from older portions of the growth.

At the present time we cannot certainly distinguish but two varieties of endothelioma of bone: (1) those derived from the endothelium of blood-vessels and perivascular lymph spaces, and (2) those springing from ordinary lymph vessels and spaces, and not immediately connected with blood-vessels. Of our own four cases, Nos. I and II belong to the first and Nos. III and IV belong to the second variety. These two varieties of tumor are characterized by unmistakable differences. The first, with their multiple rows of cells in alveolar or often in tubular arrangement, sometimes containing blood and always bounded by blood capillaries, stand out in marked contrast to the larger and smaller alveolar collections of cells which more or less completely fill the lymph spaces and lymph vessels from which their origin is so readily traced.

The second variety of bone endothelioma much resembles carcinoma in macroscopical and in microscopical appearances, and no doubt the cases of so-called primary carcinoma of bone belong to this group.

Borrmann's division of these tumors into two classes—peritheliomata and peri-endotheliomata, the first with a radial perpendicular and the second with a concentric arrangement of many layered superimposed cells about the vessel walls—is of doubtful value. The endotheliomata of bone dealt with in this article are not to be confounded with the so-called tubular perivascular sarcomata, types of which are the cases recently reported by Low and Lund.

Of the single bone tumors forming metastases in the other organs, two, as said before, had their origin from the perithelium, and two from the endothelium of lymph-space vessels. The nine cases of multiple bone tumors had their origin as follows: perithelium or blood-vessel endothelium, 6; endothelium of ordinary lymph spaces and vessels, 2; blood or lymph vessels, 1. Both of the tumors thought to be derived from the capillary endothelium and four of the peritheliomata formed multiple bone tumors, and a majority of the peritheliomata showed multiple growths.

Etiology.—Sex is without much influence; 12 cases were in males, 10 in females, and 1 sex was not recorded. These tumors occurred once each at 9, 11, 18, 25, 31, and 52 years; there were 5 cases between 40 and 50, 5 between 50 and 60, and 7 cases over 60 years. A history of previous injury was obtained in 6 cases. Further than this nothing definite is known of the cause of these growths. Without wishing to lay too much stress upon the observation, we must say that in studying sections of our Case III we were impressed with the readiness with which the proliferation of the endothelium of the lymphatics would be explained by the assumption of the action of micro-organisms or their toxines. As was necessarily the case, pictures were seen which were quite similar to those seen in the lymphatics in typhoid and other processes as pointed out by Mallory. In this connection, it is also of interest to recall the observations of the proliferation of endothelial cells of lymphatics with the formation of tubules by v. Notthaft and considered by him due to an infection in a case of pseudo-leukæmia, and the conclusions drawn by Boivard by which he excludes tumor formation in his case of splenomegaly with proliferation of the endothelium of the lymph sinuses of the spleen, abdominal lymph-glands, and perilobular lymph channels of the liver. In our own case we were struck with the idea that had micro-organisms or their toxines acted on these endothelium of the lymph vessels and sinuses, identical changes must have been produced. Micro-organisms and bodies which might be taken for them have not, however, been observed in these growths. It is to be hoped that the attention that endothelial cells are now receiving may soon throw some light upon the etiology of these growths.

Relation of endo- and peritheliomata to bone aneurisms. Pulsation of the tumors was noted in seven cases. Hildebrandt, who has carefully reviewed the subject of the relation of bone aneurisms and malignant tumors of bones, concludes that true bone aneurisms are rare, and that a pulsating bone tumor is to be regarded as malignant, probably sarcoma. Roughton, who has recently written on the subject, reaches the same conclusion.

CLINICAL (DR. CRILE).

The clinical history and aspects of endo- and peritheliomata of bone present in general a similarity to the general type of osteosarcoma. Certain differences and a few well defined distinctions are apparent on closer study. The number of cases collected (23), which for the purpose of a more minute analysis might readily be said to be insufficient, reveals in certain directions a persistence of a few distinct characteristics, so that a deduction from this compilation of the symptoms, course, and termination of these neoplasms may be fairly assumed to accord with their general clinical anamnesis.

Sex.—In the foregoing tabulation of endotheliomata of bone, the sex is given in twenty-two cases, of which twelve were males and ten females. This proportion is not in correspondence with that found by Gross in sarcoma of bones. In a collection of 149 cases of osteosarcoma, he found that men were by 17 per cent. more frequently affected.

Age.—In marked variance with sarcoma in general is the age at which endo- and peritheliomata of bone are found to occur. In ordinary sarcoma of bone, although no age is exempt, children and young adults are most frequently affected. Butlin states that young adults of both sexes, from fifteen to twenty-five years of age, are much more liable to the disease than persons at the extremes of age, while, according to Volkmann, osteosarcoma usually develop during the growth of the individual, most commonly about the twentieth year, very rarely after the fortieth. Gross, in a tabulation of 147 cases of osteosarcoma in which the age is given, found that in 68 per cent. these tumors developed before the thirtieth year, and in 32 per cent. after that period. From his table it can moreover be ascertained that 85.7 per cent. of these growths occurred before the fortieth year and but 14 per cent. after that time. Paget, in a collection of nineteen cases of osteosarcoma of various bones, reports the following:

In five	cases	the growths	occurred at	the age of	10 to 20	years.
In nine	"	"	"	"	20 to 30	"
In four	"	"	"	"	30 to 40	"
In one	case	"	"	"	40 to 50	"

To this table may be opposed that of bone endotheliomata, the comparison between the two from the similarity of numbers in both being the more striking. In a tabulation of the cases of bone endotheliomata with respect to age, one finds that:

In one	case	the growth	occurred at	the age of	9	years.
In one	"	"	"	"	11	"
In one	"	"	"	"	18	"
In one	"	"	"	"	25	"
In one	"	"	"	"	12	"
In one	"	"	"	"	31	"
In one	"	"	"	"	32	"
In four	cases	"	"	"	40 to 50	years.
In three	"	"	"	"	50 to 60	"
In six	"	"	"	"	60 to 70	"
In two	"	"	"	"	70 to 75	"

In this tabular arrangement it is to be noted that but five cases, or 26.13 per cent. of bone endotheliomata, occurred before the age of forty and 14 cases, or 73.87 per cent., after that period, while in the table of osteosarcoma of Paget, 18 cases out of 19, or 95 per cent., are found to have developed before the fortieth year, and but one case, or 5 per cent., between the fortieth and fiftieth year. In Gross's collection of 147 cases, as already mentioned, 85 per cent. occurred before the fortieth year, and 15 per cent. ofter that period. In summary:

	Before the Fortieth Year.	After the Fortieth Year.
Paget's table (osteosarcoma),	95 per cent.	5 per cent.
Gross's table (osteosarcoma),	85 per cent.	15 "
In endotheliomata of bone,	26 per cent.	73 "

As to the age, bone endotheliomata are at variance with osteosarcomata, and in accordance with carcinomata.

Cause.—In the majority of the cases there is no apparent cause. Among the cases in which the occurrence of trauma is mentioned in connection with the appearance of tumor is that of Kocher, in which a pulsating tumor with a systolic bruit developed eight months after an injury from a flail in the right frontotemporal region. In Hildebrandt's case, a male, forty-five years of age, the endothelioma was found in the lower part of the arm above a fracture of the right elbow which had been sustained in childhood. Similarly, in the case of Ritter, a female, fifty-two years old, bore the evidence of an old fracture of the tibia, above which was situated the tumor. In another case presenting primary endothelioma in the clavicle, ribs, lumbar vertebræ, the patient had sustained a fall six months previously. As a whole, injury cannot be stated to be an etiological factor of much importance.

Bones Affected.—The predilection of endotheliomata of bone like that of osteosarcoma is for the long bones of the appendicular skeleton. In the 23 cases collected, the exact position of the primary involvement is given in 20, in the other three cases a number of bones were found to have been involved, and the seat of primary origin is either not mentioned or could not be definitely determined. The various bones were affected as follows:

Humerus, 5 times; ulna, 1 time; iliac bones, 1 time; femur, 4 times; tibia, 3 times; head, 3 times; vertebral column, 2 times; sternum and ribs, 1 time; other bones, 3 times.

The appendicular skeleton was involved in 14 cases, the axial skeleton in 6 cases, a proportion of approximately 2.

1. In the appendicular skeleton the upper extremity was affected six times, the lower extremity eight times. Deducting the one case in which the iliac bones were the seat of the malignant growth, it is seen that the long bones of both the upper and lower extremity were equally affected. The single bone most frequently affected is the humerus, there being five cases out of 20, or in 25 per cent. Femur and tibia are next in the order of frequency, each being involved four times, or in 20 per cent.

In osteosarcoma the favorite seat of these malignant growths is the femur and tibia, with by far the greater preponderance in favor of the former, as can be gathered from the table of Gross. Out of 165 cases analyzed,

The femur was the seat of the disease in 67 instances.
The tibia " " " 46 "
The humerus was the seat of the disease in 25 instances.
The fibula " " " 13 "
The ulna " " " 7 "
The radius " " " 6 "
The radius and ulna were the seat of the disease in one instance.

Volkmann, in writing of osteoid or subperiosteal sarcoma, states that these growths are especially encountered in the knee ends of the femur and tibia, and Butlin says that central sarcomas attack the same bones as the subperiosteal variety, so that they may be considered in the same manner and order. He asserts that "the long bones of the lower extremity are much more liable to malignant disease than the long bones of the upper extremity; the femur and tibia are the most frequently affected of all the long bones, the tibia perhaps rather more often than the femur, while the fibula is very rarely attacked. The humerus comes next to the tibia and femur in liability to the disease; the radius is not often attacked, and the ulna so seldom that it is difficult to collect any number of cases of ulnar sarcoma. Treves gives his opinion to the effect that the bones of the lower extremities are more frequently attacked than those of the upper, probably on account of their greater liability to injury; and the lower end of the femur and upper end of the tibia are more commonly affected than the other extremities of these same bones probably for the same reason, that the knees are more often exposed to trivial injuries than any other parts of the lower limbs. In osteosarcoma it has been noteworthy that the part of the bone affected is the epiphyseal end. Senn remarks that "sarcoma is found most frequently in that part of the bone where the circulation is most active,—that is, in the epiphyseal extremities of the long bones, and in the inner layer of the periosteum, the cambium." Gross also states that sarcoma of the long bones evinces a great predilection for the articular extremities, and the majority develop in the spongy tissues of the epiphysis. In periosteal round-celled sarcomas, however, the same writer says the shafts of the long bones are much more frequently affected than the epiphyses.

In endotheliomata a similar predisposition is apparent, the site of the neoplasm being for the most part near the articular or epiphyseal extremity of the bone, where the vascular distribution is greatest. The exact position as given by the various authors is as follows:

Lücke	Humerus.	Middle.
Billroth	Tibia.	Lower half.
Schweininger	Humerus.	Not given.
V. Lukovicz	Femur.	Upper third.
Kolaczek	Tibia.	Upper part.
Hildebrandt	Humerus.	Lower end (near elbow-joint).
Driessen	Ulna.	Upper end.
Gaymard	Femur.	Upper end.
Ritter	Tibia.	Lower end.
Berger	Humerus.	Upper portion.
Crile	Humerus.	Middle third.
Crile	Femur.	Lower third.

The exact point of origin of the endotheliomatous tumors, not unlike osteosarcoma, is either from the medullary canal of long bones or the spongy tissues of flat bones, *i.e.*, central, or on the other hand from the periosteum, *i.e.*, subperiosteal. The great majority of cases are of the central variety. Such are the cases of Lücke, Billroth, Engelmann, Schweininger, Driessen, Volkmann, Berger, etc. Among the subperiosteal endotheliomata is to be noted especially the case of Jaffé. In Markwald's case, tumors of both the central and subperiosteal variety were found.

Symptoms: Pain.—The symptoms of osteo-endotheliomata are identical with those of all osteosarcomata. Pain in these neoplasms is neither constant nor present in all cases, its presence being dependent in most instances upon pressure on or on the involvement of a nervous trunk. It is for this reason variable in character, its onset, duration, degree, etc. Tanaka, in writing of the clinical symptoms of endotheliomata in general, states that these tumors usually pursue a painless course. In central endotheliomata there is probably more often pain than in the subperiosteal variety, it commonly preceding the appearance of the tumor for several weeks or months.

Tumor Formation.—The appearance of swelling or tumor formation makes itself evident at different stages of the disease. In central endotheliomata no enlargement or growth may be perceptible to either inspection or palpation, a spontaneous fracture from the erosion of bone giving the first indication of the probability of an existing neoplasm. In other cases, however, an enlargement of the affected bone becomes apparent, and especially so in the subperiosteal variety, in which the tumor formation forms the first reliable clinical symptoms. When first appearing, the tumor is of small size, and in the great majority of cases is reported on as not having increased rapidly in size, usually only attaining the size of a child's head. Pupovac states that a slow growth is characteristic of endotheliomata. In certain cases, as in those of Lukovicz and Volkmann, the growths, after having been in a state of quiescence for some time, suddenly acquired a tendency to proliferate rapidly. In Lücke's case a rapid increase in the rate of growth occurred after the bone had spontaneously fractured.

Capsule.—The demarcation between the tumor and surrounding tissues is in most instances established by a capsule. In the central growths of osteosarcoma, this capsule is either bony, membranous, or partly bony and partly membranous, while in the subperiosteal tumors it is always membranous when present. In endotheliomata of bone, the capsule, when mentioned, is usually stated to have been of a fibrous nature. Hildebrandt, however, refers to a bony capsule in bone endotheliomata, which he states to be formed from the periosteum. The statement that such a bony capsule is a new formation is somewhat problematical, as in osteosarcoma it is known to be a resulting derivative from the expansion of the cortical portion of the bone. This expansion of bone is caused by the invasion of the malignant growth, the tumor being thereby encased in a bony shell. The membranous capsule is derived from the periosteum, and probably to some extent, also, forms other connective tissues in the near vicinity of the bone and atrophied portions of muscles. Its thickness at times characterizes its most distinct attribute, which tends to hold the growth of the tumor in abeyance. Capsule formation in all endotheliomatous tumors has been frequently observed. Kolaczek, in a collection of 78 cases of endotheliomata affecting all the various tissues, states that in over one-half of these a capsule was present. Nasse, in an enumeration of 31 cases of endotheliomatous tumors of the salivary glands, asserts that in but one case was the capsule absent. Volkmann also gives the capsule a prominent position in the description of these neoplasms. The capsulation of these tumors is clinically of great importance, as it limits the growth of the new formation, and prevents early metastasis and general dissemination. When this investing membrane ruptures, the tumor may suddenly acquire rapid proliferative properties; the degree of its malignancy is thereby accordingly increased.

In their configuration these tumors correspond closely with the osteosarcomata in general, their contour being in part dependent on their situation and point of origin. In central osteosarcoma, whether situated on the epiphysis or diaphysis, a spherical or globular shape is usually found. In the subperiosteal variety, when situated on the shaft, a spindle-shaped enlargement has been more often noted when at or near the articular extremity, somewhat pyriform swelling. This variety, moreover, never enlarges the bone equally in all directions, but merely produces a swelling on one aspect, and little or none on the opposite side. In central sarcoma, the tumor formation may also affect only one side of the bone; but in other instances, the cortex of the bone becomes expanded from the pressure of the growth of the neoplasm, and it bulges out on all sides. Endotheliomata of bone conform in these characteristics with osteosarcoma. Similarly, also, in the character of their surface, which is usually smooth and even, although in certain instances it has been observed to have been lobed, nodular, or tuberous, as in the case described by Hildebrandt. At times all configuration is lost, and there results from the extensive infiltration of the contiguous tissue, as in one of our cases, a diffuse growth and somewhat general enlargement of the part.

Pulsation.—The occasional occurrence of pulsation in these tumors has in several instances, as in the case of Kocher, given rise to the erroneous diagnosis of aneurism. In this case not only was pulsation present, but also other symptoms pathognomonic of aneurism, viz., a systolic bruit compressibly of the tumor by both direct pressure, and especially upon compression of the carotid artery of that side. Ligation of the artery, moreover, caused a total disappearance of both the pulsation and systolic bruit, which persisted for twelve days, when a faint pulsation but no murmur again reappeared. In one of our own, and in other cases reported by Lücke, Jaffé, and Billroth, both a pulsation and systolic bruit were present. In other instances, however, while a pulsation is described, no mention is made of the systolic bruit or other murmurs. The great vascularity of these tumors in which pulsation was noted probably explains this occurrence. (Cases of Kocher, Jaffé, Berger, etc.) In others, as in the case of Ritter, blood spaces which communicated with each other are especially remarked upon.

Spontaneous Fracture.—Spontaneous fracture was noted in seven cases out of thirteen, in which the long bones of the appendicular skeleton were affected. Three times it occurred in the humerus and three times in the femur, and in one case, that of Berger, both the humerus and femur spontaneously fractured, the latter being the seat of metastasis. As already stated, spontaneous fracture at times gives the first indication of the existing neoplasm. It may occur without any premonitory symptoms, being the result of an erosion or pressure atrophy of the bone caused by the growth of the tumor. Theoretically, spontaneous fracture should occur only in central endotheliomata, the subperiosteal variety of these tumors, for the reason that they extend in an outward direction, and do not tend to invade the bone, and seldom, if ever, give rise to its occurrence.

Metastasis.—While Gross found that in osteosarcoma, metastasis occurred in 40.06 per cent., we note that in bone endotheliomata it is reported on in 63.64 per cent. of the cases. The organs which are most liable to metastasis are alike in all sarcomata, the lungs and the various bones of the skeleton. The spleen, liver, and lymphatic glands are more rarely affected. The greatest predilection for metastasis from endotheliomata of bone seems to be the bony skeleton; thus, in fourteen cases in which metastasis occurred, the bones were affected nine times, the lungs four times, the liver three times, and the lymphatic glands twice, and the spleen but once.

Diagnosis.—The diagnosis of osteo-endotheliomata cannot during life, from a clinical stand-point, be definitely established, as these neoplasms, as has already been repeatedly mentioned, conform in their essential characteristics with the osteosarcomata. Hildebrandt says that these tumors show no clinical differences. Symptoms entirely pathognomonic of bone endotheliomata which would serve for a differential diagnosis between the two do not exist. Among the differential characteristics may be mentioned the age at which these respective tumors are liable to appear. In patients of over forty years, it is recalled, endotheliomatous bone formations are more common in those whose age is below this period, while the reverse is the more common occurrence of endotheliomata; and the fact that numerically cases of osteosarcoma are more often found, however, counterbalances any value which may be attached to this distinction. The other symptoms, such as pain, their situation, rate of growth, nature, and configuration of the tumor, metastasis and cachexia either singly or collectively, do not clinically serve to more clearly elucidate the nature of the given growth, whether it be a sarcoma or endothelioma. From other affections with which they may be confounded, the differential diagnosis is the same as for osteosarcoma. These are carcinoma, aneurism, if pulsation and its other pathognomonic symptoms be present, other bony tumors and the various inflammatory diseases of bone, periostitis, osteomyelitis, tuberculosis, and syphilis. The diagnosis from carcinoma, even with a microscopical examination, is at times difficult, much the more so from the clinical stand-point. Aneurism, also, may in rare instances so resemble these malignant tumors that it is impossible to differentiate them. Hildebrandt and Klebs each mention a case which, from its gross appearance, was stated to be an osteo-aneurism, and microscopically shown to be an osteosarcoma.

Concerning the prognosis of bone endotheliomata, but little can be said, as the experience with the same has as yet been too scant. The prognosis may be stated as favorable in all cases in which an operative treatment can be safely instituted. In tumors of the vertebral column and in those of the base of the cranium, where incision cannot be made, the fatal course of the disease can avowedly not be arrested. Metastasis also renders the prognosis unfavorable. Tanaka says, regarding the prognosis, that it is only favorable in those cases in which it is possible to eradicate all of the diseased tissues. When a diffuse infiltration is present, the chances for a complete extirpation of the disease and an ultimate recovery are markedly increased. In such cases not only the parent growth has to be removed, but also all the metastatic processes which radiate from it and are found in the surrounding tissues.

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A CASE OF CONGENITAL HEPATOPTOSIS, SHOWING A MESOHEPAR.*

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The condition recognized as hepatoptosis is one of some rarity about which much has been written. It was first described in a postmortem examination by Heister[1] in 1754, but his article has been overlooked until recently, the credit generally being given to Cantani,[2] an Italian, who reported a case in 1866. Since his time the literature has been searched and collections of cases made by several authors, among whom may be mentioned Wickham Legg,[3] in 1878, with 20 cases; Faure,[4] in 1892, with 54 cases; Graham,[5] of Toronto, in 1895, with 68 cases, and, finally, Ssaweljew,[6] in 1903, who brings the subject practically up to date with 117 cases. Exhaustive discussions are numerous, the theses of Baget,[7] Duverney,[8] Haenselt,[9] and Pellet,[10] with the recent article of Teleky,[11] being the most complete.

By the term hepatoptosis, or floating liver, is meant a complete dislocation of the liver from its position under the diaphragm, and it does not include cases of floating lobe in which a portion of the organ remains in its normal position. The condition must be a primary affection of the liver, and not the result of intrathoracic or subphrenic abscess or tumor.

Taking this definition as our premise, we find 118 cases of complete hepatoptosis on record, 117 of which are tabulated by Ssaweljew, and 1 reported since. As to the pathogenesis of the condition, leaving out the theory of Heister,[1] promulgated in 1754, that it was due to the will of God to prove His omnipotent power, it narrows down to elongation of the ligaments, stretching of the vena cava, and congenital malformation. The condition is prone to occur in any state of laxity of the abdominal walls and decrease of the intra-abdominal tension. The direct causes given are: sex, repeated pregnancies, especially associated with a pendulous abdomen, removal of tumors, tapping of ascites, trauma, overstrain, and tight lacing. An analysis of Ssaweljew's table shows that of his 117 cases 13 occurred in men, 103 in women, and 1 in a child. Of the women 93 were married and 10 single.

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* Read before the Clinical and Pathological Section of the Cleveland Academy of Medicine, March 3, 1905.

One point in the etiology of hepatoptosis which has given rise to acrimonious discussion is the occurrence of a mesohepar. Meissner,[12] in 1869, reasoning from an analogy to floating spleen and kidney, strongly advocated on purely theoretical grounds the apposition of the two peritoneal reflections from the liver to the diaphragm, together with their lengthening as the chief factor in the etiology. His cases did not come to autopsy. Leopold,[13] in 1874, and Sutuguin,[14] in 1875, accepted Meissner's theory, but advanced nothing to prove it. In 1885 Landau,[15] basing his statement on the negative results of a large number of postmortem examinations, particularly in infants, denied the occurrence of such a structure. Faure, in his classic monograph, published in 1892, dubs Meissner's theory a pure hypothesis, and insists that it be not considered. Later writers seem to have unanimously accepted Faure's ideas.

Malformations of the liver of any grade, excepting in monsters, are rare. Numerous cases are reported in which the anomalies consist in absence of one or more ligaments, multiple lobulation, hypertrophy, atrophy, or absence of various lobes, accessory lobes, or faulty position due to rotation about an axis. More marked defects are associated with umbilical or diaphragmatic hernia.

The case we report, Louisa L., a native-born American woman, aged thirty-four years, and unmarried, was admitted to Lakeside Hospital (medical number 3854) on November 4, 1903, on the service of Dr. Powell, to whom we wish to express our thanks for permission to report the case.

The patient was admitted for pain and swelling in the right knee and ankle. In the family history the mother died of "liver trouble," and one sister of dropsy, following rheumatism. The family history beyond this was unimportant. In childhood she had had measles, mumps, and chickenpox. There was no history of pulmonary, cardiac, or gastric trouble. The appetite was good. She had always been somewhat constipated. The menstruation began at thirteen years, and had always been regular, though scanty, until three months before admission, when it stopped. She had never been pregnant. She admitted leucorrhœa for the past three or four years, but indignantly denied the possibility of venereal infection. The condition for which the patient was admitted, a subacute rheumatism, has no bearing on the present report. She had never had a serious accident or fall, and said she did not use tight corsets. Nine years before admission she first noticed a tumor in the right side of her abdomen, about the size of her fist. This did not increase in size for two years and gave her no trouble. Since then she thinks it has increased slightly and caused some dragging pain. Three years before admission an exploratory laparotomy was made by a well-known Cleveland surgeon, who diagnosed "sarcoma of the

FIG. 1

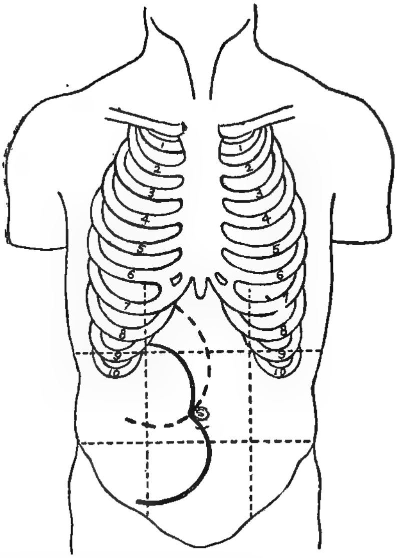


FIG. 1.—Palpation; patient on back. Black = position normally. Dotted = position with liver pushed up.

FIG. 2

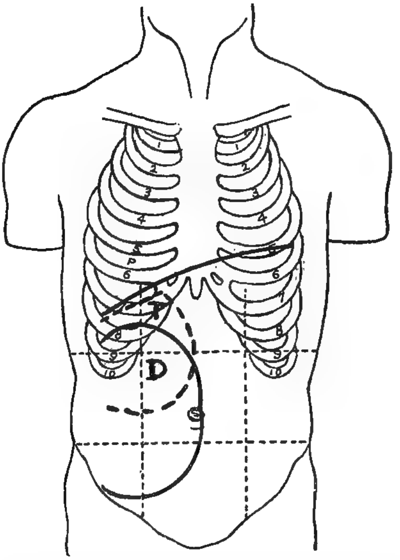


FIG. 2.—Percussion; patient on back. Black = natural position. Dotted = liver pushed up. P = pulmonary resonance. D = dulness. T = area of tympany between P and D.

FIG. 3

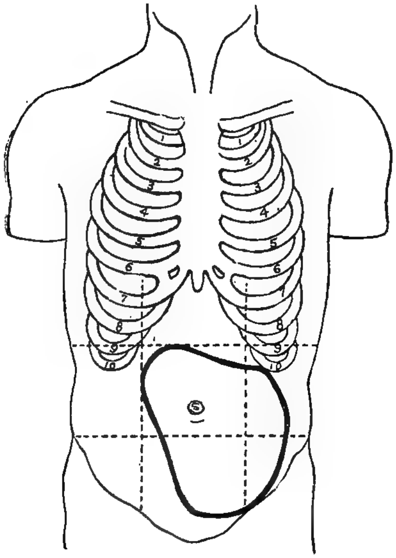


FIG. 3.—Palpation and percussion; patient on left side; position of liver.

FIG. 4

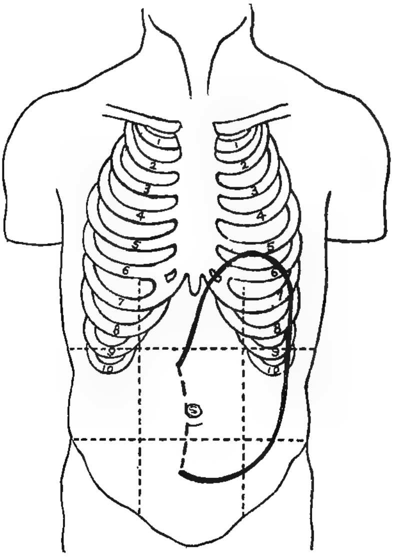


FIG. 4.—Gastric tympany; patient on back.

liver (?)" and backed out. Since then the mass has given her no trouble, except for dragging pains at times on walking. The digestion has been good.

On examination the patient is a well-nourished woman of good color. The conjunctivæ are slightly muddy, but not icteroid. The eyes are normal. The tongue is clean and moist. The teeth are in good condition. There are numerous small areas of brown pigmentation on the cheek, neck, and forearm. The thyroid is slightly enlarged and the right lobe nodular. There is no glandular enlargement. The heart and lungs are normal. The pulse is 72 per minute. The vessel wall is easily palpable.

Abdomen. The abdomen is markedly asymmetrical. There is a definite bulging in the right flank, extending from the costal border to the iliac crest. It reaches to within 2 cm. of the midline just above the navel and to the midline just below it. The mass looks smooth, except for a slight groove running directly laterally from the navel. The most prominent point is 5 cm. to the right and 2.5 cm. below the navel. The mass moves on respiration; no pulsation is seen; there is no visible peristalsis. On palpation the left side of the abdomen is soft and there are no masses felt. The left kidney is just palpable. The spleen is not felt. In the right side of the abdomen (the patient lying on her back) is felt a large, smooth, elastic mass, extending from the midline to the extreme flank. This is easily movable and can be raised by pressure in the right flank. Along the midline of the abdomen it has a definite, sharp, overhanging edge, in which, just to the right of the navel, is a distinct notch. A similar edge can be felt along the lower border. This sharp edge runs from the right anterior superior spine of the ilium in a curved line to the costal border, 4.5 cm. to the right of the midline. The mass extends in the midline 7 cm. below the navel, in the right mammary line 16 cm., and in the anterior axillary line 12 cm. below the costal border, or just to the right anterior spine. It is easily movable and can be forced to any portion of the abdomen. By pressure it can be forced upward 5.5 cm., the upper border disappearing under the costal margin. On percussion the note is flat over the tumor. In the chest pulmonary resonance reaches the seventh costal cartilage in the right parasternal line, the sixth interspace in the right mammary line, the eighth rib in the anterior axillary line, and the ninth rib in the posterior axillary line. At this line the pulmonary resonance changes abruptly to abdominal tympany. There is no liver dulness. The area of tympany extends in the right mammary line 3 cm., and is then replaced by a flat note continuous with the dull area over the tumor. When the liver is forced upward this abnormal area of tympany disappears and is replaced by dulness, which reaches from the right parasternal line to the right flank and comes directly in contact with the area of pulmonary resonance.

By placing the patient on the left side the mass falls to the left and leaves the right costal border. It then extends from the left Poupart's ligament to a point 2 cm. below the right costal border; a total distance of 24 cm., and has a width at the navel of 18 cm. In this position the left border can be easily felt in the left iliac fossa, and the sharp edge can be picked up between the thumb and finger. In this position the right border can be felt 9 cm. to the right of the navel, and is round, firm, and obtuse. From the upper right border of the mass there is felt a resistance running under the right costal border, resembling a ligament or pedicle, connecting the mass with the structures of the right hypochondrium.

On dilating the stomach by means of sodium bicarbonate and tartaric acid a prominence appears in the lower abdomen, most marked 4.5 cm. to the left and below the navel. The stomach tympany elicited by percussion and auscultatory percussion begins at the fifth interspace in the left parasternal line and extends throughout the left abdomen to a point 8 cm. below the navel in the midline, and to within 4 cm. of the left anterior superior spine of the ilium. To the right of the midline the area of tympany is encroached upon by the flatness of the tumor mass. The right kidney is indefinitely palpable in its normal position.

Vaginal examination shows a small retroflexed uterus, and no connection between the pelvic organs and the tumor mass.

There is marked swelling and tenderness of the right knee and ankle. The right heel is prominent, hard, and sensitive. The shins are clear; there is no œdema. The knee-jerks are normal.

Examination of the blood and urine shows nothing abnormal.

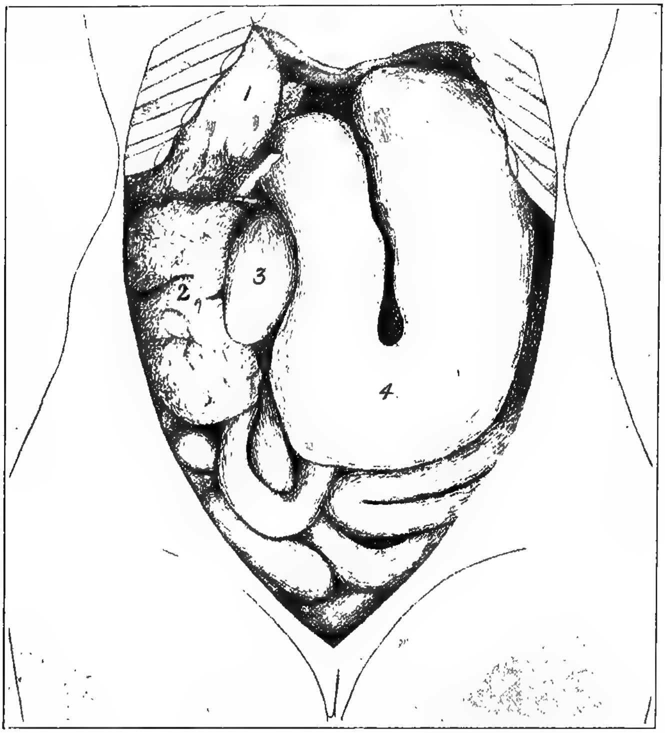
The patient received treatment for her joint trouble from November 4, 1903, to January 23, 1904, with marked improvement. Nothing was done for the liver condition, as it was giving her no trouble, until January 18th, when, on the possibility of the tumor being a gumma, potassium iodide was started in increasing doses. The temperature, pulse, and respiration all remained normal until January 24th, when, with a complaint of pain over the tumor, the temperature rose to 101° and the pulse to 100. The pain increased markedly during the next four days; the temperature rose to 104°; the pulse to 124, and the respirations to 130. An exploratory operation was performed by Dr. Dudley P. Allen on January 29th, and an acute appendicitis found. The patient died February 4, 1904. An autopsy was performed the same day.

The point of special interest in the clinical history of this case is the total absence of the accepted etiological factors in floating liver. The patient had never been pregnant, had had no accident, and had not been a heavy worker. Her abdominal walls were not especially lax. The etiological factor could not be determined during life, and the autopsy findings were required to demonstrate it as a case of congenital hepatoptosis.

Pathological Report. The following extracts are made from the autopsy protocol. The autopsy was performed two hours after death.) The body is that of an emaciated white female, 158 cm. long, with beginning rigor mortis.

The liver is displaced, lying entirely on the right side. It has two lobes—an upper, corresponding to the left, and a lower, corresponding to the right. Each lobe has a flattened and blunt, ovoid shape, the lower being nearly double the size of the upper. It extends 9.5 cm. below the xiphoid cartilage, 8 cm. below the costal margin in the mammary line, and 5.5 cm. in the anterior axillary line. The two lobes are united by an isthmus of dense fibrous tissue, which varies in width from 1.5 cm. on the right side to 3 cm. on the left, and averages 5 mm. in thickness. Scattered throughout this isthmus are isolated liver lobules, some of which are fatty. The lower lobe possesses no ligamentous attachment. The right lateral and coronary ligaments are entirely lacking. Limited to

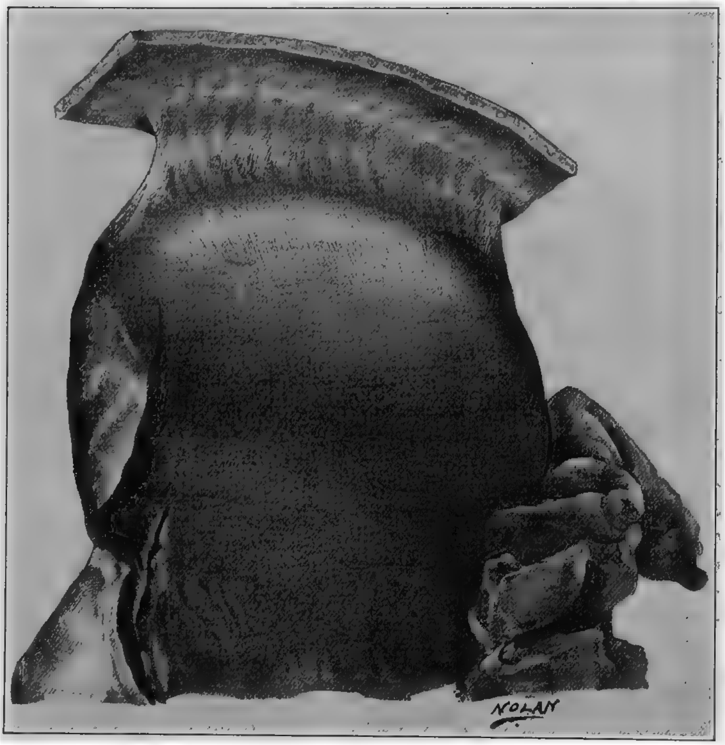
FIG. 5



Abdomen at autopsy: 1, upper (left) lobe of liver; 2, lower (right) lobe of liver; 3, gall-bladder; 4, stomach.

the upper margin of the upper lobe there is a double reflection of peritoneum to the diaphragm. The liver itself does not touch the diaphragm, and the mesohepar thus formed is 13 mm. in length. The two peritoneal reflections are united only at their free edges, enclosing a space 1 cm. in width at the surface of the liver and a few millimetres at the diaphragm, which is filled with lax fibrous tissue. From the upper half of the right margin of the upper lobe, along the natural line of reflection of the left lateral ligament, there extend lax and easily torn fibres to the diaphragm. These are regarded as adhesions. The suspensory ligament, instead of being attached along the longitudinal fissure, touches the interlobar isthmus only at its left margin, but it is also attached along the left border of the upper lobe. The round ligament also joins the interlobar isthmus at its left margin. A thick zone of fibrous and fatty tissue, with isolated nodes of liver parenchyma, lies posterior to the junction of the suspensory ligament with the upper lobe. The hepatorenal fold of peritoneum joins the liver at the interlobar isthmus.

FIG. 6



Upper lobe, showing attachment to diaphragm by mesohepar.

The fissure of the gall-bladder appears as an ovoid depression, 4 cm. long, in its normal position with reference to the lower lobe, but its long axis coincides with the long axis of the lobe. The transverse fissure is represented by a deep notch in the upper posterior margin of the lower lobe, from which two fissures branch at an acute angle. The left branch, which is 4 cm. long, is parallel to the gall-bladder fissure and 1.5 cm. from it. The right branch, which is longer, is poorly defined at its origin, but deep at its extremiyt. The subdivisions of the right branch of the portal enter these fissures. The hepatic ducts leave the liver and the hepatic artery and the portal vein enter it at the left margin of the interlobar isthmus. The artery divides 4 cm. and the vein 5 cm. before entering the liver. The relative position of these vessels is normal. The fissure of the vena cava crosses the left posterior upper extremity of the upper lobe. The umbilical fissure and the fissure of the ductus venosus are lost in the separation of the lobes. The quadrate lobe is probably represented by the portion between the gall-bladder fissure and the left branch of the transverse fissure. The caudate and Spigelian lobes have necessarily no analogues.

The liver weighs 1385 grams. The upper lobe measures 13.8x 10.8 x 6 cm., the lower 17.5 x 11.5 x 8 cm. The liver capsule is moderately thickened. The surface of the lower lobe is finely nodular, but that of the upper is more smooth. The lower lobe cuts with greatly increased resistance, and its cut surface is granular. The lobules vary much in size. There is a distinct increase of interlobular fibrous tissue. The liver tissue is of a dull brownish-yellow color. Over the surface and throughout the organ are scattered minute bright-yellow areas. The upper lobe has a smooth surface on section, its resistance is but slightly increased, and the tissue is flabby in consistence. Occupying the centre of the upper lobe is an irregular mass of mixed pearly and translucent fibrous tissue, having the shape of a three-pointed star. One point extends nearly to the left margin, while the other two extend only half-way to the right. Throughout the mass are scattered irregular nodules, varying in size from a few millimetres to 1 cm. in diameter. These project above the cut surface and consist of a firm but friable and structureless tissue of a homogeneous yellow color.

The gall-bladder, which is much enlarged, is U-shaped, and lies between the stomach and the lower lobe of the liver. The distal arm, which is more distended, lies anteriorly. It is 9 cm. long and 5 cm. in diameter. The proximal arm is the same length, but gradually narrows to the orifice of the cystic duct. The organ is not adherent.

The stomach also has a U-shape and is enormously dilated. It extends 11 cm. below the xiphoid cartilage. The cardiac arm of the U measures 22.5 cm. in length and the pyloric arm 16.5 cm. The diameter at the cardiac end is 19 cm., at the middle 9.5 cm., from which the size diminishes gradually to the pylorus. The pylorus is in its normal position.

The appendix is absent and closure of the wound of operation is not perfect, intestinal contents exuding from a minute hole. In the right ileocæcal region the intestinal surfaces are united by fibrinous exudate and have a dark necrotic appearance. Similar exudate is found in moderate amount over the liver and the spleen. There is a scanty amount of brownish, turbid fluid free in the peritoneal cavity. The transverse colon is prolapsed and collapsed, and lies behind both liver and stomach.

The mucosa of an area, with a diameter of 4 to 6 cm. about the orifice of the appendix, is ulcerated. The ulcers have an irregular shape, with a sloping edge and a necrotic floor. The intervening tissue is intensely congested. The mucosa of the rest of the cæcum and colon is smooth, but indurated and mottled with dark-brown pigmentation. The remaining viscera are normal in their positions.

Microscopic. Sections from the new-formed tissue in the upper lobe of the liver show typical gummata. The periportal tissue is especially increased in the lower lobe, with atrophy and necrosis of the liver cells. Periarteritis and endarteritis are well marked.

There are extensive areas of coagulation necrosis and purulent infiltration in the mucosa and submucosa of the cæcum. Some ulcers extend to the submucosa. The acute process is so well marked as to obscure any old lesions, but in the submucosa of the colon are areas of vascular and well-organized granulation tissue, with extensive proliferation of the adventitia of the small arterioles. Some larger arterioles are occluded by a recent endarteritis. An enormous amount of a coarse brownish pigment is deposited in the mucosa of the large intestine, both in cells and free. It does not give an iron reaction.

Pathological Diagnosis. Congenital malformation and displacement of the liver; multiple gummata of the liver, with syphilitic cirrhosis; chronic passive congestion of the portal system; operative removal of the appendix; acute general peritonitis; dilatation of the stomach with atrophic gastritis; acute ulcerative typhlitis; chronic enterocolitis; syphilitic endarteritis and periarteritis of the large intestine; hypertrophy of the thyroid; tuberculosis of the tracheal glands.

We are indebted to Dr. W. T. Howard, Jr., for the use of material and for his supervision of the work.

CONCLUSIONS. 1. The abnormal position of the liver, with its limited mobility, its atypical shape, the absence of the coronary and right lateral ligaments, the abnormal origin of the left lateral ligament, which assumes the function of the coronary ligament, and of the suspensory and round ligaments, the shifting of the fissure of the vena cava from one lobe to the other, though the course of the vessel is normal, together with other variations, leave no doubt as to the embryonic origin of the condition. Syphilis was merely a coincidence.

2. As the review of the literature, particularly of the references given in the *Anatomischer Anzeiger* for the past fifteen years, and of the collections of Jacquemot[16] and Faure,[4] shows no identical case, and but one slightly resembling the present one, it must be considered as unique.

3. The case, though it does not prove that a mesohepar is the cause of hepatoptosis, does prove Meissner's hypothesis that such a condition may exist.

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Extracted from the American Journal of the Medical Sciences, October, 1905

A PROCEDURE FOR OPENING THE PERICARDIUM.

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It is a well-attested fact that pericarditis is recognized much more frequently at the postmortem examination than during life. That it is difficult to recognize no one will gainsay, as many of the cases develop during the last hours of life as complications of some other diseases; then, some cases which might be recognized are overlooked because the patient is too ill to justify a thorough physical examination. In 4700 cases of the medical service of the Lakeside Hospital there have been diagnosed some 45 cases of pericarditis, of which 13 were fatal—a mortality percentage of 29. In the same service there were 245 cases of pneumonia, with a mortality of 29 per cent., while in 15 cases complicated by pericarditis there was a mortality of 71 per cent., an increase of over 40 per cent. in the complicated cases. There were 158 cases of acute articular rheumatism treated, with a death rate of 3½ per cent.; while in 9 cases complicated by pericarditis mortality was 30 per cent. This shows from the clinical side what a marked increase of deaths occur in the two diseases with which pericarditis is most commonly associated, if they are complicated by it.

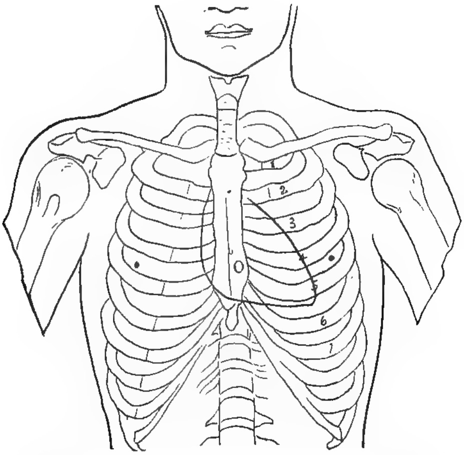
It may seem that one who has been working along pathological lines is afield in developing an operation, but that is a logical origin. My experience at the autopsy table has impressed on me three points in regard to pericarditis: (1) its great frequency as a complication of other diseases; (2) the comparative ease with which the pericardium may be explored through an opening in the sternum; (3) the necessity of local treatment in severe cases. It seems to me that if advantage is taken of the anatomical relation of the pericardium to the posterior surface of the sternum, there is afforded an easy route of attacking the pericardium and applying local treatment in suitable cases.

The treatment of the pericardium should be the same as that of other serous cavities—viz., joints. In simple conditions, rest and local application of ice-bag or heat. When there is no reaction to this treatment, it is aspirated when there is simple effusion, and opened when pus is present. These procedures should also be applied to the pericardium in similar cases.

I have been impressed, as I lifted the sternum after severing the ribs on either side during postmortem examination, by the broad connection of the posterior surface of the lower one-third of the sternum with the anterior surface of the pericardium. The pleuræ form the lateral boundaries to this tissue of the anterior mediastinum. This forms, what it seems to me, a feasible route for attacking the pericardium, as it has a correct anatomical basis. A layer of prepericardial fat, which sometimes contains lymphatic glands, normally separates the sternum and pericardium.

In some pathological conditions, as with adherent obliterative pericarditis, fibrous tissue invades this fatty tissue, and then the pericardium is bound to the sternum. The size and shape of this area vary. Voinitch and Sionojensky have worked out a composite picture of the cases in their experience. It forms a triangle, with the base lying to the left of the midline and opposite the fifth intercostal space, and the apex extending down the fifth intercostal space. While I have not worked out a composite picture, I have found but a single case in 110 autopsies that has failed to have a connection that one would miss by going through the sternum at this point. This was in a child aged eight years, with a pigeon-shaped breast. Using this connection as a basis, I have developed the following procedure for entering the pericardium.

FIG. 1

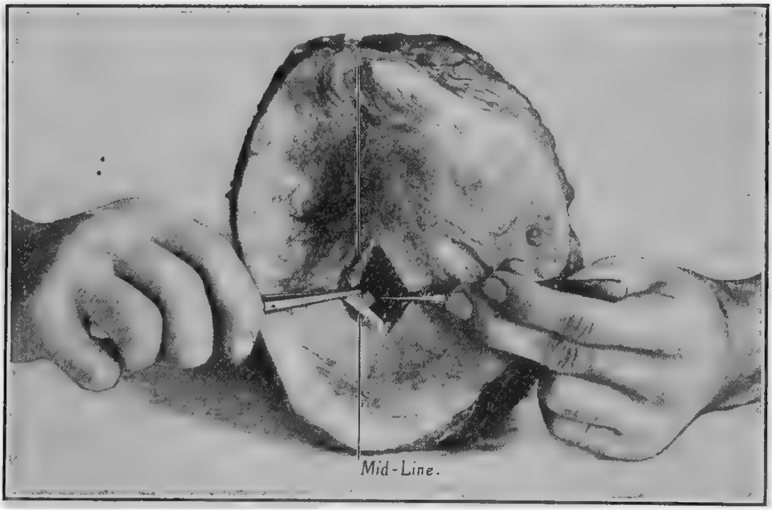


Position of pericardium and window in sternum.

A skin incision is made parallel to the mid-line of the sternum and ½ cm. to its left, extending from the level of the upper border of the fifth costal cartilage to the lower border of the sixth. This incision is deepened until the sternum is exposed. This is laid bare over an area of 2.5 cm. and the periosteum is raised.

With a trephine, 2 cm. in diameter, a circular window is made through the bone in the same manner as in trephining the skull. One opens upon the anterior mediastinum and the prepericardial fat then comes to view. The fat is dissected away and the anterior surface of the parietal pericardium is exposed. The pericardium is raised by two mouse-toothed forceps, and an incision is made between them. From this opening into the pericardium, which is at its lowest level, just above its union with the diaphragm, one can readily explore the pericardial cavity, and then institute the treatment that is necessary, according to the conditions present. In children the sternum is narrower, and one may make the incision nearer the midline, so that the trephine opening will not separate a rib from the sternum. I have found one case in which the sternum, in the adult, was just 2.5 cm. in width. The internal mammary artery lies from $\frac{1}{2}$ to 2 cm. beyond the sternum, and so it is not injured. The sternum averages about $\frac{3}{4}$ cm. in thickness in the adult, but varies considerably. I have had one case, and have seen several, in which there was an opening in the sternum at the level of the fifth intercostal space, about $\frac{3}{4}$ cm. in diameter. This condition is due to a developmental error (lack of fusion of two sides in the embryo).

FIG. 2



Photograph of specimen. Pericardium held by forceps.

After one has trephined it is best in those cases where there is pus to fill the cellular portion of the cut edge of the bone with a 15 per cent. iodoform wax, to guard against infecting the bone and to aid in stopping (any excess of) hemorrhage. When the anterior mediastinum is entered one may find some enlarged lymph nodes. I have found some as large as lima-beans in cases of pneumonia. These should be excised with the fat. When the pericardium is bared it can be identified by feeling the heart beating, and its convexity will be caudal-ward. In those cases where the diaphragm is raised above the normal position by pressure from below, the convexity will be cephal-ward. The pleuræ may be distinguished on either side by the color. In purulent cases it is well to place a purse-string suture before incising the pericardium. A rubber catheter is inserted to aid in flushing and should be left for drainage. Gauze should be packed around the catheter to protect the anterior mediastinum. Better drainage will be afforded if the patient is turned on the right side. (The after-treatment will depend on conditions found and their reaction to drainage and flushing with warm saline.)

The advantages presented by this procedure:

1. It is anatomically correct.
2. Easy approach to the pericardium by definite landmarks that are readily made out.
3. The best possible drainage afforded.
4. It permits of ready inspection of the heart and the pericardial cavity.
5. It is devoid of mechanical danger, such as hemorrhage and rupture of the pleura.
6. It can be done under gas anæsthesia.
7. It requires but five to fifteen minutes for its completion.
8. No after-deformity.
9. Least possible danger of spreading infection to the pleural cavities or to the peritoneum.

The advantages and the relative simplicity of the operation are such that the opening of the pericardium should become more frequent. In the height of our present knowledge it seems conservative to treat all cases of purulent pericarditis and large serous effusions, and those cases of fibrinous pericarditis not reacting to rest and the ice-bag by drainage. Cases should be operated upon earlier in the disease before myocarditis has developed from absorption of toxins.

I have performed this operation on eighteen autopsy subjects. Once on a dog, in which I infected the pericardium, manipulated the heart roughly, and simply left drainage to see what would result. Estimated hemorrhage was 5 c.c. The dog was quite sick for five days, then rapidly improved. In two weeks only a healing wound remained. I have made some recent observations on the position of the heart in effusion and the relations of the pericardium to the thorax while under tension, which will be reported later.

Extracted from the American Journal of the Medical Sciences, December, 1905

FURTHER OBSERVATIONS ON THE RELATION OF LESIONS OF THE GASSERIAN AND POSTERIOR ROOT GANGLIA TO HERPES OCCURRING IN PNEUMONIA AND CEREBROSPINAL MENINGITIS.[1]

By William Travis Howard, Jr., M.D.,
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Introduction. At the meeting of the Association in 1902 I reported two cases of herpes, one of the lip and nose and the other of the trunk, occurring in acute croupous pneumonia, in both of which the sensory ganglia supplying the areas affected with herpes showed acute degenerative and exudative changes.

At this time I suggested that careful examination would disclose similar lesions in the sensory ganglia supplying areas affected with herpes, complicating other infectious diseases, especially cerebrospinal meningitis, typhoid fever, and malaria.

Since then I have had opportunity to examine at autopsy two cases of cerebrospinal meningitis and one case of pneumonia with herpes. In all three cases definite lesions were found in the sensory ganglia supplying the herpetic areas.

In addition, I have seen in the wards of the Lakeside Hospital, in the service of my colleague, Dr. John H. Lowman, two unusual examples of facial herpes complicating non-fatal pneumonia.

Report of Cases: Herpes Complicating Pneumonia.

Case I. *Summary: Herpes of the skin of the right side of the nose, especially marked near the inner canthus of the right eye, occurring in a child with pneumonia complicating typhoid fever; degenerative and exudative changes in that portion of the right Gasserian ganglion, giving rise to the nerves supplying the skin of the upper portion of the nose; left Gasserian ganglion normal.*— T. W., male, aged four years, was admitted on March 26, 1903, to the Lakeside Hospital, service of Dr. John H. Lowman, after an illness of thirteen days. He was drowsy and apathetic and breathed rapidly. Physical examination showed signs of consolidation of the upper lobe of the right lung. The spleen was enlarged. Widal reaction positive. There was a well-marked crop of herpes near the inner canthus of the right eye. On the morning of March 31st sloughing of the right cornea was recorded. Death occurred at 11.45 P.M., March 31, 1903.

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[1] Read by title at the Twentieth Annual Meeting of the Association of American Physicians, Washington, D. C., May 17, 1905.

Clinical Diagnosis. Typhoid fever, acute croupous pneumonia of the right lung, herpes of the right side of the nose, sloughing of the right cornea.

Anatomical Diagnosis. Typhoid fever (ileotyphus), hyperplasia of the mesenteric lymph nodes and the spleen, acute croupous pneumonia of the right lung (all three lobes), acute serofibrinous pleurisy, emphysema of the left lung, focal necrosis of the liver, cloudy swelling of the heart, liver, and kidneys. Herpes of the right side of the nose, sloughing of the right cornea, congestion, hemorrhage and acute degenerative and interstitial inflammation of the right Gasserian ganglion.

Bacillus typhosus was isolated from the spleen and gall-bladder, and staphylococcus pyogenes aureus from the lungs, heart blood, and liver.

The autopsy was begun ten hours after death. The detailed description of the autopsy findings will be omitted. The Gasserian ganglia were of ordinary size. The veins about both were congested. The capsules and nerves of both were free from signs of inflammatory exudation. There was no meningitis.

Histological Examination of the Gasserian Ganglion and the Fifth Nerve. Right Gasserian Ganglion: There was marked congestion of the veins along the convex border of the ganglion. Here, corresponding to a portion of the origin of the superior maxillary muscle of the fifth nerve, there was an area showing marked degeneration of the ganglion cells and infiltration of the interstitial tissue with leukocytes. The fifth nerve and its branches showed no degenerative or inflammatory changes. The *left Gasserian ganglion* and fifth nerve were normal.

CASE II. *Summary: Herpes of the right upper and lower lips, the right upper and lower eyelids, and the right side of the neck*—i. e., *of the regions supplied by the right Gasserian and the right third cervical ganglia, occurring during an attack of acute croupous pneumonia, ending in recovery.*—Mrs. H. C., aged fifty-eight years, was admitted to the Lakeside Hospital, service of Dr. J. H. Lowman, on May 7, 1904, with the physical signs of acute croupous pneumonia of the lower lobe of the right lung, which later involved the entire lung. She was taken ill on May 3d, with a chill and pain in the right side of the chest. On admission there was an extensive crop of herpes involving both the upper and lower lips (most marked on the right side) and the right upper and lower lids of the right eye. There was conjunctivitis with granular lids on this side.

On the sixth day of her illness a crop of herpes appeared on the right side of the neck two inches below the angle of the jaw.

The patient recovered, so there was no opportunity to examine the sensory ganglia. The herpes ran the usual course of the so-called herpes zoster. In the light of our previous cases and of those of meningitis reported below, it is evident that the patient had extensive lesions of the right Gasserian and of the right third cervical posterior root ganglia.

CASE III. *Summary: Herpes of the left lower eyelid occurring in the course of acute croupous pneumonia.*—In this man, also in the service of Dr. J. H. Lowman, there was herpes orbicularis occurring in a typical attack of acute croupous pneumonia, ending in recovery.

Herpes Complicating Cerebrospinal Meningitis.

CASE IV. *Summary: Epidemic cerebrospinal meningitis, with herpes of the right side of the face and neck, and of the left upper lip, and the vestibule of the nose and of the head and soft palate, regions supplied by both Gasserian and the third right cervical posterior root ganglia.*—D. L., male, aged twenty years, entered the Lakeside Hospital, service of Dr. H. H. Powell, October 27, 1904, complaining of severe pain in the head and the right side of the body. He had always been well until October 20th, when he was taken ill with chilly sensations and pain in the head and body.

Four days later he suffered severe burning pain in the right side of the neck. Later at this point a rash developed, followed by a large crop of herpetic vesicles. On admission there was marked rigidity of the neck, hyperæsthesia, and marked herpes, involving a large area on the right side of the neck below the angle of the jaw. Herpes later developed on the right cheek, near the ear. Kernig's sign was present. The diplococcus intracellularis meningitidis was isolated from fluid removed at lumbar puncture. Death occurred November 11, 1904.

Clinical Diagnosis. Epidemic cerebrospinal meningitis with facial and cervical herpes.

Autopsy. The autopsy was begun one hour after death.

The following is abstracted from the autopsy protocol: The body is that of a white male, 167 cm. long. There are extensive herpetic eruptions involving the right cheek just in front of the ear, the right side of the neck, the left upper lip and vestibule of the left nostril and the mucous membrane of the hard and soft palate on both sides. The eruption of the lip and nose is in the vesicular stage. That on the face and neck is covered with dry crusts. In the mouth the eruption is macular and pustular.

Nervous System. The dura and pia arachnoid are congested. Over the surfaces of the medulla and pons there is a thick fibrinopurulent exudate of gelatinous consistency. At the base of the brain and in the lateral ventricles there is a considerable amount of turbid fluid. The nerves at the base of the brain are enveloped in the exudate.

Gasserian Ganglia. Both are surrounded by a thick purulent exudate. The bloodvessels are congested.

Spinal Cord. The membranes of the cord are bathed in a turbid fluid. The pia arachnoid is covered with a fibrinopurulent exudate, which extends to many of the nerve roots. The cord on section shows no appreciable changes. The third right cervical ganglion is larger than its fellows of the opposite side.

The other organs show no changes of present interest and their description is, therefore, omitted. The diplococcus intracellularis meningitidis was isolated in pure culture from the cerebrospinal exudate.

Microscopic Examination of Nervous System. The central part of the convex border of the ganglion—*i. e.*, that portion corresponding to the origin of the superior maxillary branch and possibly a portion of the inferior maxillary branch is the seat of extensive degeneration and destruction of ganglion cells, with leukocytic infiltration.

The affected ganglion cells are cloudy, stain poorly and are often hyaline. Some cells are swollen and others are shrunken. In those less affected the nuclei show no changes. In markedly degenerated cells the nuclei may be eccentric and some stain diffusely. The leukocytic infiltration is most marked in the interstitial tissue, but some ganglion cell spaces contain leukocytes. The plexus of nerve fibres coming from this portion of the ganglion are surrounded with a fibrinopurulent exudate. Sections of the sensory root of the fifth nerve show no recognizable changes, when stained in either methylene blue and eosin or by Weigert's myelin sheath method.

Left Gasserian Ganglion and Fifth Nerve. In this ganglion similar changes are present and in the same portion of the ganglion as described in the right. The sensory root of the fifth nerve shows small scattered areas of cellular infiltration.

The Third Right and Left Cervical Ganglion and Posterior Root Nerves. The right ganglion is the seat of numerous small areas of ganglion cell degeneration and of interstitial and periganglion cell cellular infiltration. The changes are best marked at the distal end and at one side of the ganglion. The right posterior root is surrounded and infiltrated by large numbers of leukocytes. The left posterior root is similarly but less intensely affected. The left ganglion is normal.

Sections of the cord made at various levels show marked meningiis. The other ganglia are free from changes.

Anatomical Diagnosis. Acute epidemic cerebrospinal meningitis, due to diplococcus intracellularis meningitidis. Degenerative and exudative changes in both Gasserian and in the third right Gasserian ganglia, herpes of the hard and soft palate, the left upper lip, the vestibule of the nose, the right cheek and the right side of the neck.

In regard to the lesions in the third right cervical ganglion, it is clear that the infection made its way along the posterior nerve roots. In the case of the Gasserian ganglia the route of the infection is not so clear, but it is evident that the inflammatory process is more marked in the nerve bundles about the ganglion than in the latter structure itself. It is to be noted that the distribution of the herpetic lesions corresponds exactly with the ganglionic lesions.

CASE V. *Summary: Trifacial neuralgia of the right side, suppuration of the sphenoidal sinuses; brain abscess and acute cerebrospinal meningitis, due to an actinomyces; herpes of the posterior and lateral cervical regions of the side.*—E. W., coachman, aged forty-six years, was admitted on February 11, 1905, to the Lakeside Hospital, service of Dr. J. H. Lowman, complaining of severe trifacial neuralgia of the right side. He denied having had any previous illness, except whooping-cough in childhood. He stated that he had been in good health until two weeks before admission, when his illness began with severe headache and backache. There was a slight chill, but no cough or other symptoms of disease of the respiratory tract. Ten days before admission he developed some pain, paroxysmal in character, and tenderness on pressure of the right side of the face and head. Remedies applied in the hospital relieved this pain.

On February 13th, two days after admission, he developed symptoms pointing to brain abscess on the right side and to cerebrospinal meningitis. At lumbar puncture 70 c.c. of turbid fluid were obtained. From the fluid Dr. Louis W. Ladd isolated an actinomyces, which will be described in a future paper.

At this time there appeared well-marked herpes of the skin over the capital portion of the trapezius muscle and the angle of the scapula on the left side. There was no herpes elsewhere. Death occurred February 17, 1905.

Clinical Diagnosis. Abscess of the right side of the brain, cerebrospinal meningitis due to an actinomyces. Herpes of the neck.

Autopsy. The autopsy was begun a few hours after death. As this case will be reported in full in another paper, the present descriptions of the pathological findings will be restricted to the lesions of the right fifth nerve and Gasserian ganglion and the third and fourth cervical ganglia and their roots.

Abstract of the Autopsy Protocol. The right Gasserian ganglion is of ordinary size. The sensory nerve of the fifth nerve is swollen and is marked by dark-red streaks. The veins about the ganglia were markedly dilated.

Histological Examination. Some of the veins of the capsule of the ganglion are found to be congested, but there is no hemorrhage. The ganglion cells stain normally, are not shrunken or invaded by cells. There is no infiltration of the interstitial tissue. In sections of the root of the fifth nerve stained with eosin and methylene blue, marked inflammatory lesions are found. The small veins and capillaries are congested and widely dilated. There are numerous areas of hemorrhage, which distort the nerve tissue. In many sections there are large accumulations of red blood corpuscles, leukocytes, and large oval cells about the dilated bloodvessels. The large cells, which are most numerous are evidently proliferated connective-tissue cells. In sections stained by Weigert's myelin sheath method, there is marked breaking up and even disappearance of myelin sheaths about many of the fibres about the areas of hemorrhage and inflammation. The left Gasserian ganglion and fifth nerve show no pathological changes.

Third Cervical Ganglia and Posterior Roots. The left ganglion is larger than its fellow of the opposite side. Histologically, the changes are marked. They consist in degenerated and necrotic changes in ganglion cells and in proliferative and exudative changes in the interstitial tissue. The changes are confined largely to the proximal end and to one side of the ganglion. In the affected areas the capillaries and small veins are dilated, and here and there small areas of hemorrhage are seen. The degenerative changes of the ganglion cells vary from swelling and cloudiness, with failure of the granules to stain, to hyaline change and complete necrosis. Some cells show larger and smaller vacuoles. The necrotic cells are shrunken, and their nuclei do not stain. The nuclei of some of the degenerated cells stain diffusely. There is proliferation of the cells of the spaces about the ganglion cells. The latter are not, however, invaded by cells. The right ganglion is normal.

Posterior Nerve Root. Left. The inflammatory changes here are extreme. The nerve is surrounded by a thick fibrinopurulent exudate, and in many places there are larger and smaller areas of purulent exudation in the nerve itself. This is associated with both hemorrhages and proliferation of nerve cells. Similar but less intense changes are found in the right posterior root.

The Fourth Cervical Ganglia and Nerve Root. The left ganglia and its root show the same marked degenerated and inflammatory changes described in the third left. The right ganglia is normal, but its root shows marked perineuritis and endoneuritis. The other ganglia are normal.

Spinal Cord and Meninges. Sections of the cord and meninges cut at various levels show meningeal inflammation in varying degree. They are most marked at the level of the third and fourth cervical ganglia. Here the pia arachnoid is the seat of a marked fibrinopurulent exudation, which extends along the nerve roots on both sides. The polymorphonuclear neutrophilic leukocyte is the most common cell in the exudate, but large and small mononuclear leukocytes are also present. There are also numbers of large cells with single oval nuclei. A few long, thread-like organisms are found.

The cord shows no inflammatory changes, and its ganglion cells appear normal.

Anatomical Diagnosis. Actinomycotic abscess of the right occipital lobe rupturing into the right lateral ventricle. Suppurative inflammation of the sphenoidal sinuses, acute seropurulent cerebrospinal meningitis. Acute neuritis of the fifth nerve and of the third and fourth and other posterior nerve roots. Acute inflammation of the third and fourth posterior root ganglia of the left side; herpes of the left side of the back of the neck and of the left scapular region. Slight actinomycotic bronchopneumonia.

SUMMARY. A review of these cases shows a complete correspondence between the situation of the herpetic lesions and the ganglionic changes. In each case the distribution of the herpes was limited to areas of skin or mucous membrane supplied by the ganglia, which were the seat of the degenerative inflammatory lesions. In those cases with herpes of areas supplied by nerves from the Gasserian ganglion this relation is even more precise. In Case I., for instance, with herpes on the nose near the inner canthus of the eye, the ganglionic lesion was limited to the point of origin of the superior maxillary nerve. In Case IV., with multiple herpetic lesions of the head (nose, upper lip, cheek, hard and soft palate), the lesions of the Gasserian ganglia again corresponded completely to the portion giving origin to the nerves supplying these parts. In Cases II. and III., though unsupported by anatomical examination, in view of the findings in the other cases, the inference that the herpes was associated with lesions of the Gasserian ganglia seems justified.

Case V. is of particular interest, for it demonstrates that, just as in spinal meningitis with involvement of the nerve roots, herpes does not occur unless the inflammatory changes extend to the ganglia; so in marked neuritis of the sensory root of the right fifth nerve, without appreciable changes in the Gasserian ganglion, herpes of the part supplied by this ganglion does not occur. In this case, under these conditions, there was severe trifacial neuralgia without herpes. Degenerative changes, with or without inflammatory lesions of the sensory ganglia, are therefore necessary for the excitation of the nervous impulses upon which the production of the herpetic lesions depend.

Cases IV. and V. also confirm the opinion expressed in my previous paper that the herpes of cerebrospinal meningitis is due to inflammatory lesions of the sensory ganglia.

The cases reported in this article furnish additional proof to support the position that the ordinary herpes zoster, as well as the herpes of pneumonia and cerebrospinal meningitis, is a pathological condition dependent upon definite lesions of certain sensory ganglia, which may be caused by a variety of agents acting in different ways. The herpes is dependent upon the ganglionic lesions, and apparently does not vary with causes of the latter, whether they are due to embolism, thrombosis, hemorrhage, invasion by tumors, microorganisms and other toxins or to other poisons. The ganglionic changes in the cases of herpes complicating pneumonia and cerebrospinal meningitis studied by me are identical with those described by Head and Campbell in their acute cases of so-called spontaneous herpes zoster. In the herpes of meningitis the ganglion changes are probably commonly due, as pointed out by Councilman, Mallory, and Wright, to an extension of the inflammatory process along the nerve roots to the ganglia. In pneumonia the matrices morbi are apparently brought to the ganglia by the circulation.

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THE FREQUENCY AND ETIOLOGY OF ACUTE NONTUBERCULOUS PNEUMONIA IN A GENERAL HOSPITAL.[1]

BY

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An examination of the index-catalog of the autopsy records of the pathologic laboratory of the Lakeside Hospital showed such frequent occurrence of acute nontuberculous pneumonia at autopsy, that I made a critical analysis of the relative frequency and the causes, both predisposing and determining, of this affection.

This hospital has about 225 beds, divided into medical, surgical, gynecologic, and private ward services, all of which are active, and, in general, receive only acutely ill patients. These patients represent all classes of society. About two-thirds of the deaths come to autopsy.

This study is based upon a series of 550 consecutive autopsies, which cover a period of about seven years. All doubtful cases and all cases of simple bronchitis are excluded. The diagnosis in every case is based upon microscopic as well as upon macroscopic examination. The autopsy technic is exhaustive, and the microscopic as well as the macroscopic appearances of the various organs are recorded in the protocols.

The routine bacteriologic investigation includes coverslip preparations from all exudates, and plate and other cultures from the heart, lungs, gallbladder, liver, spleen, kidneys, and exudates. The cultures are worked out with care.

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[1] Read by title at the twentieth annual meeting of the Association of American Physicians, Washington, D. C., May 17, 1905

The pneumonias are classified according to the usual custom into croupous or lobar, and broncho or lobular.

The 550 consecutive autopsies furnish 195 instances of acute nontuberculous pneumonia, an incidence of 35.45%.

The cases of pneumonia are naturally grouped under several headings.

1. Primary pneumonia (for which the patients were brought to the hospital and admitted as cases of pneumonia), 35, or 6.36% of the total number of autopsies.

(*a*) Acute croupous pneumonia, 31 cases.

(*b*) Acute bronchopneumonia, 4 cases.

2. Secondary pneumonia (developing in the hospital as a complication of some other disease for which the patient was admitted, as typhoid fever, appendicitis, nephritis, arteriosclerosis, injuries, etc. Many of these cases are "terminal infections,") 160 cases or 29% of the autopsies.

(*a*) Acute croupous pneumonia, 36 cases.

(*b*) Acute bronchopneumonia, 124 cases.

1. The primary pneumonias present nothing of special interest.

Group *a* primary croupous pneumonia, 31 cases, in which pneumococcus occurred alone in 25, and with streptococcus in 2; streptococcus was found alone in 1, and with *B. mucosus capsulatus* in 1; *Staphylococcus pyogenes aureus* was isolated in pure culture in 2. Pneumococcus was probably present in the 4 cases in which we failed to find it; for, as is well known, this organism often fails to grow in cultures, and is not always found in coverslip preparations from exudates, from which cultures give positive results. In 10 cases there was arteriosclerosis, and in 10, nephritis. The former was the most marked lesion in 8, and the latter in 5 cases.

Group *b* primary bronchopneumonia, 4 cases; pneumococcus was found alone in 3 and *Streptococcus pyogenes* alone in 1. All these cases occurred in young persons. One had chronic glomerulonephritis.

2. Secondary and often terminal pneumonias, 160 cases, 29% of the autopsies.

Group *a* secondary croupous pneumonia, 36 cases, 6.5% of the whole number of autopsies. Pneumococcus occurred alone in 19 cases, with *Staphylococcus pyogenes aureus* in 2, and with *B. typhosus* in 1. *Streptococcus pyogenes* was found alone in 2, *Staphylococcus pyogenes aureus* alone in 4 and *B. mucosus capsulatus* in 3. *B. coli* occurred alone in 1. In 5 cases there is no record of the isolation of bacteria. It is quite probable that pneumococcus was or had been present and was overlooked for the reasons given.

In this group of cases arteriosclerosis was present in 17 and chronic nephritis in 20.

Many of these cases were examples of terminal pneumonia developing in the course of serious and usually chronic visceral disease. These were in the order of their importance, arteriosclerosis 10, chronic nephritis 3, cirrhosis of the liver, brain tumor, cerebral hemorrhage, epilepsy, gunshot wound of the brain, myocarditis, cholecystitis, chronic dysentery, carcinoma of the breast, 1 case each. There were 2 cases of carcinoma of the stomach, in one of which operation was done. The cases of cholecystitis, gunshot of the brain, the carcinoma of the breast, were the only other cases in which operation was done. Of the remaining 13 cases, there were 5 of typhoid fever (in 2 of which operation was performed for perforation), 3 of appendicitis with peritonitis (operation in all), 1 of gunshot of the abdomen with peritonitis, 1 of puerperal infection, 1 of carbolic acid poisoning, and 2 of morphin poisoning.

Group *b* secondary bronchopneumonia, 124 cases or 22.5% of the autopsies. Cultures were positive in 120 cases.

Tables giving occurrence of bacteria in secondary bronchopneumonia.

TABLE I.

Giving total number of cases in which the various bacteria were present.

	Cases.
Pneumococcus	25
Staphylococcus	30
Streptococcus	23
B. mucosus capsulatus	35
B. coli	16
B. typhosus	2
B. influenzæ	2
B. diphtheriæ	1

TABLE II.

Showing occurrence of pneumococcus.

	Cases.
Pneumococcus alone	16
Pneumococcus and streptococcus	2
Pneumococcus and staphylococcus	1
Pneumococcus, streptococcus and staphylococcus	1
Pneumococcus, streptococcus and B. mucosus capsulatus	2
Pneumococcus and B. coli	2
Pneumococcus and B. influenzæ	1
Total	25

TABLE III.

Showing occurrence of *Staphylococcus pyogenes aureus*

	Cases.
Staphylococcus alone	18
Staphylococcus and streptococcus	5
Staphylococcus and pneumococcus	1
Staphylococcus, pneumococcus and B. typhosus	1
Staphylococcus and B. coli	2
Staphylococcus , B. coli and B. mucosus capsulatus	1
Staphylococcus and pneumococcus	1
Total	29

TABLE IV.

Showing occurrence of *Streptococcus pyogenes.*

	Cases.
Streptococcus alone	13
Streptococcus and staphylococcus	5
Streptococcus, staphylococcus and B. typhosus	1
Streptococcus and B. coli	1
Streptococcus and pneumococcus	2
Streptococcus and B. mucosus capsulatus	1
Total	23

TABLE V.

Showing occurrence of *B. mucosus capsulatus.*

	Cases.
B. mucosus capsulatus alone	30
B. mucosus capsulatus, pneumococcus and streptococcus	2
B. mucosus capsulatus and staphylococcus	2
B. mucosus capsulatus and streptococcus	1
Total	35

TABLE VI.

Showing occurrence of *B. coli*

	Cases.
B. coli alone	11
B. coli and streptococcus	1
B. coli and pneumococcus	2
B. coli and staphylococcus	2
Total	16

TABLE VII.

Showing occurrence of other organisms.

	Cases.
B. influenzæ alone	1
B. influenzæ and pneumococcus	1
B. typhosus alone	1
B. typhosus, streptococcus and staphylococcus	1
B. diphtheriæ alone	1
Total	5

It is difficult to estimate the importance to be given to *Bacillus coli* as a cause of pneumonia. It was the only organism found in 11 cases. It is probable that in at least some of the cases one or more other organisms may have been present and overlooked. It is interesting to observe, however, that of these 11 cases the primary disease was intestinal obstruction in 2, typhoid fever with perforative peritonitis in 1, and cholecystitis in 3. There was peritonitis in 9 of the 11 cases.

Of far greater interest, however, is the analysis of the primary diseases in which this series of bronchopneumonia was secondary. The following tables give the incidence of bronchopneumonia in connection with various diseases:

TABLE VIII.

Acute infections.

	Cases.
Typhoid fever	22
Meningitis	5
Phlegmon of subcutaneous tissues	5
Diphtheria	4
Acute endometritis (after abortion)	5
Umbilical infections	3
Pertussis	2
Empyema	3
Purpura hæmorrhagica	1
Enterocolitis	2
Tetanus	1
Pemphigus	1
Appendicitis	2
Total	56

TABLE IX.

Noninflammatory affections of the nervous system.

	Cases.
Injury to the brain (fracture of skull)	3
Injury to the cord (fracture of vertebras)	2
Cerebral hemorrhage	2
Cerebral tumor	2
Total	9

TABLE X.

Diseases of the liver and biliary system.

	Cases.
Cirrhosis	2
Acute yellow atrophy	1
Abscess	1
Cholecystitis (abscess of liver in one case)	4
Dilation of biliary passages and obstructive jaundice	4
Total	12

TABLE XI.

Certain diseases of the intestines.

	Cases.
Ulcers of the colon	1
Strangulated hernia	1
Intestinal obstruction (all with peritonitis at operation)	4
Total	6

TABLE XII.

Other affections.

	Cases.
Arteriosclerosis, the most marked chronic lesion	12
Chronic nephritis, the most marked chronic lesion	3
Morphin poisoning	3
Carbolic acid poisoning	1
Thrombosis of large veins	2
Diabetic gangrene (amputation)	1
Extirpation of spleen (after injury)	1
Multiple fractures	2
Carcinoma of esophagus (rupture into trachea)	1
Tuboovarian abscess (chronic)	3
Pyonephrosis (death 11 days after suprapubic cystotomy)	1
Cardiac disease	8
Total	38

In the following cases, bronchopneumonia developed after operation in individuals who had no apparent previous focus of infection:

TABLE XIII.

	Cases.
Gastroenterostomy	1
Carcinoma of neck (tracheotomy)	1
Carcinoma, ovary	1
Total	3

SUMMARY.

It will be noted that 76, or about 61% of these cases occurred in individuals with acute infectious processes. Of the 43 autopsies in typhoid fever cases in this series, 22 of the subjects had had bronchopneumonia and 5 croupous pneumonia. Of 81 cases of peritonitis from all causes, 36 of the subjects or 44.4% had had pneumonia. A study of these cases does not indicate that operation in peritonitis increases the incidence of pneumonia. This point, however, needs further study. In all the cases of diphtheria and pertussis coming to autopsy, there had been pneumonia. There were no autopsies in cases of scarlatina, measles, or variola.

Individuals with chronic nephritis and arteriosclerosis are apparently more likely to have croupous than bronchopneumonia as a terminal infection. Thus of 36 cases of secondary croupous pneumonia, arteriosclerosis was the most marked chronic lesion in 10 and chronic nephritis in 3, while of 124 cases of secondary bronchopneumonia, arteriosclerosis was the most marked lesion in 12, and chronic nephritis in 3.

It is of interest that *B. typhosus* was obtained from the exudate in two cases of bronchopneumonia and in one of croupous pneumonia in typhoid fever. It is doubtful, of course, if it held any etiologic relation to the pneumonia, as it is commonly present in the blood in typhoid fever, and the typhoid bacilli present in the cultures from the lungs may have come from the pulmonary bloodvessels. Of the 21 cases of appendicitis coming to autopsy, only 5 of the subjects showed pneumonia, 3 croupous and 2 bronchopneumonia.

In the secondary pneumonias associated with acute infectious processes it is not always possible to determine whether the organisms reach the lung by inspiration or by the blood. Those associated with streptococcus infections and many of the staphylococcus and colon bacillus infections, especially cases of septic endometritis, peritonitis, and wound infections, are commonly embolic, while those due to pneumococcus and *B. mucosus capsulatus* are probably, in most cases at least, examples of inhalation pneumonia. The pneumonias of typhoid fever are commonly inhalation pneumonias and are caused by a variety of organisms. In the croupous pneumonia of typhoid fever, pneumococcus occurred in 4 out of 5 cases, in 2 alone, in 1 with *B. typhosus*, and in 1 with staphylococcus and streptococcus. In the bronchopneumonias of typhoid fever the bacteria found were:

	Cases.
B. mucosus capsulatus alone	9
B mucosus capsulatus, pneumococcus, and streptococcus	1
Pneumococcus alone	1
Pneumococcus and streptococcus	1
Pneumococcus and B. coli	1
B. typhosus alone	1
B. typhosus, streptococcus, and staphylococcus	1
Streptococcus and staphylococcus	1
Undetermined	8
Total	24

In many of the secondary cases the areas of pneumonia were not extensive; this was especially true of the bronchopneumonias, in which the process would have often been overlooked but for routine microscopic examination of the lungs. Since over 50% of our autopsies on typhoid fever subjects showed pneumonia, it would be of interest to know the proportion of patients with this disease who have pneumonia and recover. The clinical diagnosis of pneumonia was not made in many of the secondary or terminal cases; this is readily explained by the occurrence of the pneumonic process in patients so seriously ill with some primary disease that the disturbance entailed by a careful physical examination of the chest was not justified. It is evident that in a considerable number of these cases the complicating pneumonia had little influence upon the lethal issue, occurring, as it so often did, during the last hours of individuals destined to die of the primary disease for which they entered the hospital. In another class of cases, however, it is clear that the complicating pneumonia turned the scale and carried off patients who would otherwise have recovered, or in chronic diseases, have improved. In some of the cases there was general infection with pyogenic organisms, which probably played a more serious part than the pulmonary affection. There are in the records, however, a considerable number of cases of chronic visceral disease, arteriosclerosis, and chronic nephritis especially, with terminal general infections without pneumonia, which are not, of course, included in the present paper.

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CONGENITAL MALFORMATION OF THE ESOPHAGUS, WITH REPORT OF A CASE.

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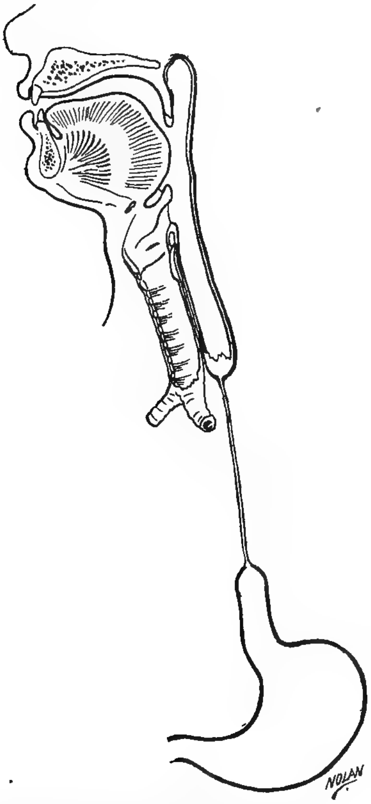
The case I wish to report is that of a male white infant two days old, admitted to the Lakeside Hospital, August 13th, on the service of Dr. Henry S. Upson, to whom I am indebted for the privilege of reporting this case. Family history throws no light on the case. Though the presentation was normal, the labor was moderately difficult, forceps having been used. It took about thirty minutes after birth to resuscitate the child, who did not cry at all loudly for twenty-four hours, and showed no inclination to nurse. When fed with a medicine-dropper he would make an attempt to swallow, but the liquid, mixed with frothy mucus, would be regurgitated through the nose and mouth. Urination was normal, and meconium was passed during the first four days. After this, there was no bowel movement, and practically no urine was excreted.

Physical examination showed him to be a full-term child, weighing 4½ pounds. His face, hands and feet showed some cyanosis. He lay very quietly either on his back or right side, and would cry feebly if much disturbed. The fontanels, eyes, ears, nose and mouth were normal. From the nose and mouth considerable white frothy mucus escaped. The neck showed no rigidity, and there was no retraction of the head or glandular enlargement. The chest was well formed, but the breathing was shallow and somewhat labored. The costal margins showed a peculiar quivering motion during inspiration, which was prolonged. Slight impairment of resonance was found over both lungs posteriorly. The breath sounds could be feebly heard throughout the entire chest. The heart, abdomen, genitals, anus and extremities were apparently normal.

On giving the child water with a medicine-dropper the white frothy mucus from the nostrils and mouth increased, the breathing became more difficult, and, for a short time, the infant became very cyanotic. A soft rubber catheter was passed down the pharynx and esophagus and it stopped at a distance of 10 cm. from the gums. Two days before death a few fine moist râles were heard over the posterior part of both lungs. The child gradually grew weaker, his weight dropped to 3 pounds and 14 ounces, and he died on the ninth day after birth.

A postmortem examination was made ten hours after death by Dr. David Marine, whose report on the findings I have abbreviated below.



SCHEMATIC DRAWING SHOWING THE CONDITION EXISTING IN THE CASE PRESENTED.

On removing the tongue, pharynx and stomach *en masse,* it was found that the pharynx ended blindly 5 cm. below the base of the epiglottis, making a funnel-shaped pouch. In the gross there was no vestige of esophageal tissue visible below the pouch, there being only a thin mass of homogeneous fibrous tissue for 5 cm. along the aorta. Then extending from the cardiac end of the stomach was another blind tube which appeared to be the normal cardiac end of the esophagus, ending in a bag-like pouch.

The stomach was fetal, being a cylindrical tube 2 cm. in diameter, contracted and containing only a little stringy brown mucus. The intestine was normal, anatomically, 1 cm. in diameter, and contained only a small amount of mucus; the bile ducts were patent.

The thyroid was firm, dark red in color and enlarged symmetrically.

The kidneys were fused below, the fused portion crossing the middle line on the body of the second lumbar vertebra.

The right lung showed patchy consolidation in the posterior part of the upper lobe.

Microscopically, a section of the prevertebral tissue taken just below the blind end of the pharyngeal pouch showed a mass of smooth muscle tissue, the fibers of which were for the most part arranged longitudinally and surrounded by a vascular fibrous sheath. Near one edge of this muscular bundle were two masses of squamous epithelium with distinct lumina. They were placed side by side, but each epithelial mass was surrounded by its own fibro-muscular sheath. These two areas were taken for esophageal epithelium and were considered remnants of imperfect development. A section of the prevertebral tissue below this showed no vestige of esophageal elements.

Congenital malformation of the esophagus is a comparatively rare condition. The earliest recorded case is that of Durston in 1670. In 1880 Mackenzie carefully searched all the literature previous to that date and he was able to find 62 examples of this anomaly. In 1886 Solis-Cohen was able to find records of only 4 cases reported in this country, to which Marsh in 1902 added another. Recent additions to the literature of this condition have been made by Steele, Dickie and others. Dickie in 1906 says that he could find only 13 cases that had been reported since Mackenzie's scrutiny. However, it is probable that many examples of this anomaly are overlooked, for Hirschsprung, writing in 1860, mentioned 4 cases that he had personally observed in seven months in a town of only 180,000 inhabitants. Mackenzie suggests that if stillborn infants, and especially monsters, were subjected to careful postmortem examinations, this anomaly would be more frequently observed.

There is a remarkable uniformity in this abnormality. Of the 62 cases collected by Mackenzie, in 43 there was an intercommunication between the esophagus and the air passages with deficiency of a portion of the former, the communication being with the trachea in 40, and with one of the bronchi in 3. Of intercommunication between the esophagus and trachea, the esophagus being otherwise normal, there were 2 cases. Of blind termination, Mackenzie found 9, and of complete deficiency 5 examples on record. Marsh claims that 2 of these cases of complete deficiency, viz., those of Lozach and Heath, do not properly belong to this category. He claims that Lozach's case is the history of the dissection of a monstrosity with many anomalies, yet gives no very definite reason why it should not be included in this class. He states conclusively that the case of Heath was an example of congenital absence of the duodenum. Excluding these 2 cases, the 3 remaining, together with those reported by Steele and Marsh, make in all 5 cases of congenital absence of the entire esophagus. Of complete membranous obstruction of the esophagus there are 2 cases. Blasius has reported 1 case of longitudinal division of the esophagus.

Marsh gives the following classification of the malformations of the esophagus:—

1. There may be a congenital fistula of the neck, due to a want of closure between the second and third branchial arches and involving the esophagus.
2. The esophagus may be completely absent.
3. The esophagus may be obliterated only in certain portions of its extent.
4. There may be stenosis not amounting to complete obstruction.
5. There may be dilatation or diverticula.
6. There may be a fistulous communication with the trachea or with a bronchus.
7. There may be a double esophagus with reunion at the cardiac end.

In very few instances is this anomaly not associated with some other deformity. Of this condition, Mackenzie says: "In 1 instance there were spina bifida, absence of the anus, and a single horseshoe kidney placed over the spine. In 2 cases there was trifurcation of the trachea, and in 2 others there was pulmonary atelectasis. In another case the stomach and intestines were contracted. The other deformities associated in different cases with esophageal inosculation were: Malformation of the uterus, combination of the male and female genital organs; imperforate anus with a communication between the intestines and the bladder and deformity of the pelvis; absence of the right lung and atresia ani; imperforate anus with intercommunication between bladder and rectum, deficiency of the radius in each arm, and clubbed hands; imperforated anus with intercommunication between rectum and urethra and right auriculo-ventricular opening almost blocked by membranous diaphragm.

In only 3 instances is it expressly stated that there was no other deformity; while in 19 cases there is either no mention of the condition of the other organs, or it is formally stated they were not examined.

No very satisfactory explanation has yet been advanced for this defect. It cannot be due to a failure of communication between the primitive buccal cavity and the mesenteron, for His has shown that if a line be drawn from the arch of the lower jaw to the pouch of Rathke, this will represent the dividing line between the stomodeum and the structures of hypoblastic origin. Probably the best explanation is that given by Shattock in 1890 and quoted by Dickie in 1906. The former says: "In atresia of the esophagus it is the growth of the diverticulum from the anterior wall of the mesenteron (from which diverticulum are developed the lower part of the trachea and the lungs), which, by displacing forwards the hind wall of the mesenteron, leads conceivably to the secondary closure of the latter, *i.e.*, of the esophagus." In support of this is the anatomical fact that the esophagus diminishes in calibre at the level of the fourth dorsal vertebra. The larynx is usually unaffected, as it is developed independently of the pulmonary diverticulum.

The symptoms are so typical that the condition will at once be recognized. The child at birth may appear perfectly normal and attempt to nurse, but the milk will not be swallowed. If milk is given with a medicine-dropper it will precipitate a distressing attack of suffocation, the child becomes very cyanosed and the milk mixed with frothy mucus will be regurgitated through the mouth and nose. If a catheter be passed down the pharynx, the site of the obstruction will be revealed and the diagnosis confirmed. Meconium will be passed the first two or three days after birth, but after that time there is no bowel excretion. The infant gradually weakens, dying of exhaustion.

The cases invariably end fatally, the duration of life depending upon the vigor of the child at birth, the average being four or five days. The longest time recorded was twelve days. Gastrostomy has been tried in some cases, but unsuccessfully.

Since this paper was written, an infant three days old was admitted to Lakeside Hospital February 29, 1908, on the surgical service of Dr. Allen, with symptoms similar to those described in my case. The child died two days later and autopsy revealed the absence of a little more than one-third of the esophagus. No other malformation was present.

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THE RELATION OF IODIN TO THE STRUCTURE OF THE THYROID GLAND.

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INTRODUCTION.

The analyses and experiments embodied in this paper comprise the second stage of the work on the nature of goiter, viz.: the relation of iodin to the structure of the thyroid gland.

In previous papers one of us[1] discussed the structure of the thyroid in its various phases in the attempt to formulate basic anatomic types to which the individual glands could be referred. It was found that the various types of changes are quite easily separated into four natural groups, viz.:

(1) Normal glands.

(2) Glandular hyperplasias, all degrees (parenchymatous hypertrophies).

(3) Colloid glands, goiter (all degrees).

(4) Complications supervening in any of the three preceding groups.

It has also been pointed out[2] that the anatomic changes observed in developing goiters are of such nature, and occur under such peculiar conditions, and can be controlled by such particular procedures, that we are forced to conclude that they are physiologic reactions to some deficiency, or compensatory hyperplasias.

Among the factors which might be connected with this deficiency, iodin was rendered most prominent by the observations of Halsted[3] on compensatory hypertrophy, by the discovery of Baumann[4] of the normal presence of iodin in the thyroid and by the vast accumulation of clinical and experimental evidence of the specific therapeutic effect of iodin in the hyperplasic or parenchymatous glands. We were, therefore, led to investigate further the relation of iodin to the gland structure. This work, so ably begun by Baumann[5] and others, undoubtedly lost much of its real worth by their attempts to apply the discoveries to analogous conditions in the human being before the difficulties and complicating conditions were fully recognized. Moreover, as the discovery of iodin came at the time when the chemistry of thyroid opotherapy was attracting the attention of other physiologic chemists who were more particularly interested in the organic constituents of thyroid proteids, the views of the above-mentioned investigators (Baumann, Oswald,[6] Roos[7]) as to the relation and importance of iodin in the proteid molecule met great opposition.[8]

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[1] Cleveland Med. Jour., 1907, vi, p. 45; also Johns Hopkins Hosp. Bull., 1907, xviii, 359.

[2] Jour. Infect. Dis., Chicago, 1907, iv, 417; also Cleveland Med. Jour., 1908, vii, 105.

[3] Halsted, W. S., Johns Hopkins Hosp. Rep., 1896, i, 373; also Med. Rec., N. Y., 1888, xxxiv, 368.

[4] Ztschr. f. physiol. Chem., 1896, xxi, 319.

R. Hutchinson[9] asserts that the activity of the thyroid is due to the two proteids of the colloid, but, after examining them in the light of Baumann's work, he found that both contain iodin, adding that one has only to realize the small amount of iodin (a few mgm.) to recognize that it can not play an active part. Concluding, he says: "The colloid matter then is the active substance—the part which iodin plays it plays by virtue of the form of combination in which it occurs in the colloid and not by virtue of its being iodin." In a second paper[10] he still considers iodin of secondary importance to the proteids in the therapeutic value of thyroid extract, and adds that if iodin in the colloid be increased ten times, as it is possible to do, it does not increase its activity.

To-day, however, one feature is generally agreed on, viz.: that the physiologic activity of the (colloid) thyreoglobulin is dependent on the amount of iodin contained in organic combination. Hunt[11] has recently arrived at similar conclusions in a novel way—that of testing the resistance of animals to a poison (acetonitrile) with and without the administration of thyreoglobulin.

In this work we have attempted to eliminate as many of the complicating, perplexing and uncertain factors as our present knowledge would permit, and to include all the factors which were open to observation and which at the time seemed to have a bearing on the structure or chemistry of the gland. With this idea in view, we chose to use the dog and have appended the full table of analysis, the special features of which will be pointed out under their appropriate headings.

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[5] Ztschr. f. physiol. Chem., Strassb., 1896-7, xxii, 1; also Baumann and Roos, ibid, 1896, xxi, 480.

[6] Ibid., 1897, xxiii, 265; also Inaug. Diss., Strassb., 1900.

[7] Ibid., 1896, xxi, 19; also Virchow's Archiv., 1902, clxix, 444.

[8] Notkin, Wien. med. Wchnschr., 1895, xlv, S. 824; 872; also Fränkel, S., Wien. klin. Wchnschr., 1895, viii, 842; also Med. Record, N. Y., 1896, xlix, 37.

[9] Jour. Physiol., 1896, xx, 474.

[10] Jour. Physiol., 1898, xxiii, 178.

[11] The Journal A. M. A., 1907, xlix, 1323.

The general views as to the etiology of goiter may be divided into two groups: (1) that it is due to an infecting agent (miasm) and (2) that it is the manifestation of a nutritional disturbance. The former had its period of greatest development parallel with the early period of bacteriology (1850-1885). Virchow, Hirsch and, in particular, Ewald have supported this view.

The latter view, that it is a nutritional disturbance, has received its greatest support from experimental investigations. The experiments, accidental, as it were, of the elder Kocher, and Reverdin,[12] of the total removal of the gland in man, were probably the most suggestive in the early period. The work of Munk[13] on the importance of the thyroid gland to the animal, pointing to conclusions which were so contradictory to the prevailing views[14], stimulated Halsted,[3] in the early days of aseptic surgery, to repeat them. Halsted's fundamental experiments and observations, followed by those of Horsley[15] and Edmunds,[16] have established several important general biologic facts, chief among which are: (1) that the gland is essential to normal body economy; (2) that partial removal is followed by compensatory hyperplasia of the remaining portion; (3) that myxedematous conditions follow the total removal of the thyroid gland alone, and (4) that it is possible to produce experimentally congenital (goiter) hyperplasia of the thyroid.

The introduction of thyroid feeding into the treatment of myxedema and later into that of goiter, in general, was particularly associated with the names of Murray[17] and Mackenzie[18] in England and Bruns[19] in Germany. Advances in our knowledge of the chemistry of the gland followed quickly on the discovery of its therapeutic merits and are in particular associated with Hutchinson,[9] Fränkel,[8] Baumann,[5] Oswald[6] and Roos.[7]

The results of all the investigations included in the above summary have tended to show (1) that the thyroid gland is an organ essential to the normal metabolic activities of the animal; (2) that it probably has a definite secretion; (3) that iodin is an essential constituent of this secretion, and (4) that the various anatomic changes occurring in the gland are results of or reactions against general nutritional disturbances rather than specifically thyroid in origin.

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[12] Quoted in report of the committee on myxedema, Trans. Clin. Soc., Lond., 1888, No. 21.

[13] Sitzungsber. d. k.-preuss. Akad. d. Wissensch. zu Berlin, 1887.

[14] Schiff, Arch. f. exp. Path. u. Pharmakol., 1884, xviii, 25.

[15] Brit. Med. Jour., Lond., 1895, i, 111, 211; also Internat. Beitr. z. Wissensch. Med., 1891, i, 369.

[16] Jour. Path. and Bacteriol., Lond., 1894-6, iii, 488.

[17] Lancet, Lond., 1893, i, 1130.

[18] Ibid., 123.

[19] Beitr. z. klin. Chir., 1894, xii, 847.

ANATOMIC CONSIDERATIONS.

The trite phrase, that "our knowledge of structure must precede our knowledge of function," seems particularly applicable to the study of the thyroid. Indeed, in our experience, the thyroid gland offers one of the most striking examples yet encountered of the relationship between variations in physiologic activity and in anatomic structure. In this work, a classification of the thyroid changes that is at once simple of application, well defined, and as free from vagueness as possible is absolutely essential. The present state of our knowledge offers no condition or factor, other than structure, that is sufficiently constant or uniform to allow of its use as a basis of classification. By examining large numbers of thyroids, it has been found possible to differentiate types to which the various grades and stages of the changes can be made to conform. Thus, by making as few subdivisions of these pure types as is possible the existing confusion in nomenclature may be obviated to a large extent. We also think that the anatomic standard of classification in experimental work on the thyroid will permit comparisons with other observers' work which, at present, is not possible. Such a classification will allow us to refer all phases of the subject under investigation to a fairly constant anatomic base-line and render possible an analytic study of these phases.

The material for this work consists of the thyroid glands of a series of over one hundred dogs taken without discrimination as to weight, age, sex or breed from the several department laboratories. Care was taken, however, to get the thyroids as soon as possible after the dogs were brought from the street in order that the findings might with justice be taken as an index of the normal street condition. As factors which might conceivably affect the condition of the thyroid, we observed the age, sex, breed, weight and state of nutrition. Records were made of all these conditions, though as regards age and breed gross errors are probable. The thyroid glands were weighed fresh; brief descriptions of color, consistency and visible colloid were noted; a small piece for microscopic

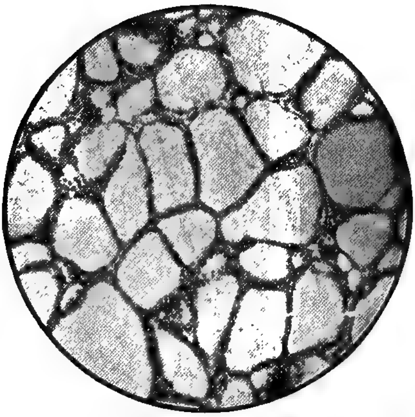

Fig. 1.—Normal thyroid, dog.

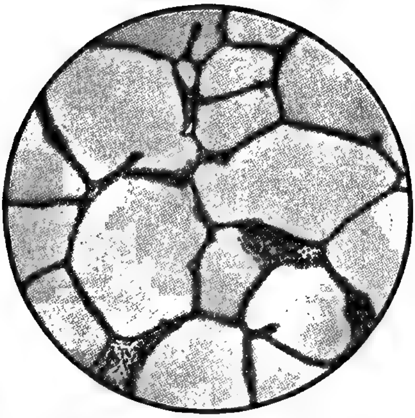

Fig. 3.—Colloid gland (goiter), dog.

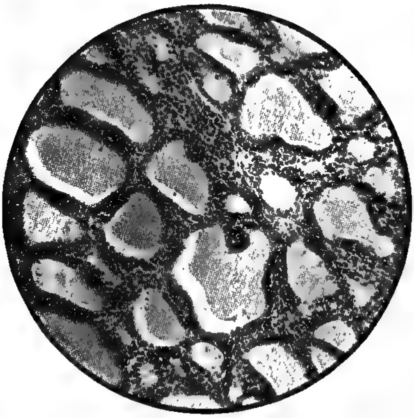

Fig. 4.—Early glandular hyperplasia, dog.

examination was then removed, and the gland reweighed and referred to Dr. Williams for iodin determination.[20]

As a result of an extensive experience with the anatomic appearances of the dog's thyroid, we have found that, while in general one can make fairly accurate determinations as to the type and even the grade of change from the gross appearance, there is always the chance for error; e. g., small glands may show quite marked hyperplastic changes, though, as a rule, the enlargement is proportional to the degree of glandular hyperplasia. Likewise, while the color and consistency and blood vessels, in general, conform to the glandular changes, reliance on them may be a source of error, as pointed out by Halsted.[3] The microscopic appearance, therefore, has been our sole final guide to the group or subgroup to which each gland was referred.

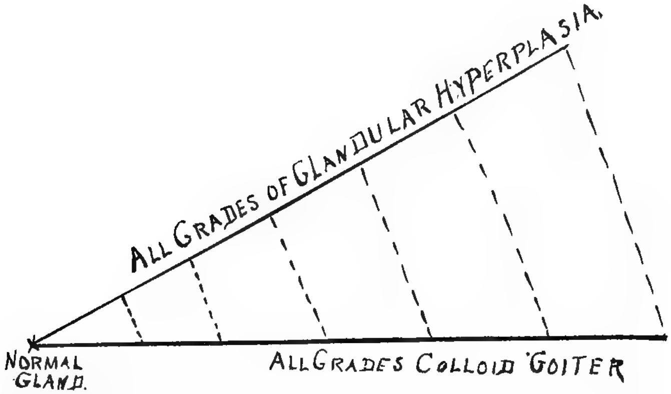
All Grades of Glandular Hyperplasia.
Normal Gland.
All Grades Colloid Goiter

Fig. 2.—Showing relation of glandular hyperplasia to colloid goiter.

Barring complications, the three natural groups are, as previously stated: (1) normal glands, (2) colloid glands, (3) hyperplastic glands. Subgroups have been made only of Group 3—the glandular hyperplasias. It was further found necessary to make double reference to several of the glands, as *"normal X early," "colloid X early," "early X moderate,"* or *"moderate X marked."* These will be considered as intermediate groups. Brief anatomic descriptions of the groups and subgroups follow:

GROUP 1. *Normal Gland.*—The normal gland is similar, as to all its essential anatomic features, in all mammals examined. In herbivora, as a rule, the gland has coarser lobulations and more stroma. In the dog, the normal gland has a thin gray translucent capsule. The gland tissue is firm and of a yellow translucent color, due to the abundance of syrupy colloid. The blood and lymph vessels are very small. Microscopically, the acini are rounded, fairly regular spaces, lined by a single layer of flat cubical epithelium. The epithelial nuclei are small, flattened and darkly staining. The colloid is quite uniform and homogeneous in its staining reaction and sharply abuts on the lining epithelium. The stroma is very scanty. All glands conforming to this description were considered normal (Fig. 1). Glands to which there are double references are not included in the analytical tables. In our series there were but three[21] glands (A-38-87-98) which conformed to this rigorous standard—two from females and one from a male. All three dogs were in a fair state of general nutrition. Regarding age and breed there is nothing significant.

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[20] The iodin determinations were made quite independently of the histologic work, and the anatomic groupings were made independently of the iodin determinations.

GROUP 2. *Colloid Gland.*—The colloid gland (goiter) in its uncomplicated form may be considered as an exaggeration of all the normal gland structures. Since it has been shown definitely by one of us that practically, if not quite all, colloid glands (goiters) have been preceded by a hyperplastic stage and are to be considered as the reverted and quiescent or as nearly the normal state as a gland can ever become which has once been the seat of a glandular hyperplasia, it then follows that we have to deal with all grades of the colloid condition, depending on the degree of hyperplasia preceding it. We think it necessary to consider all thyroids as colloid glands if they show any microscopic evidence of having had any grade of glandular hyperplasia preceding, no matter if their size, color, consistency and general appearance at the time of obtaining coincide with those of a normal gland. This view is shown more clearly in Figure 2.

To take, then, a moderate example of a colloid gland, the anatomic findings are as follows: The gland is symmetrically enlarged and very firm, the capsule is somewhat thickened and opaque, while the acini are large, well defined and filled with clear yellowish colloid. The tissue is translucent and not vascular. Microscopically, the arteries show an obliterating endarteritis similar to that occurring in the uterine or thymic vessels during involution. The colloid stains uniformly and densely and abuts sharply on the epithelium. The acinar epithelium is flat-cubical and arranged in a single layer. The nuclei are flattened, small and darkly staining. Depending on the degree of preceding glandular hyperplasia and on the duration of the colloid stage, there are more or less numerous sprigs of acinar epithelium jutting into the lumina of the acini, which are the remnants of the invaginations and plications of the epithelium during the hyperplastic stage. As may be inferred from Figure 2, there are stages in the process of reversion when it would be impossible to decide whether the histologic changes are to be considered progressive or reversive; hence, there is some difficulty of determining even histologically whether a given specimen ought to be considered with the colloids or with the hyperplasias.

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[21] The findings of but three absolutely normal glands out of the 113 specimens is due to the very rigid standard of normal adopted, viz., the seacoast type. Many ordinarily called normal were classified in the intermediate groups, i. e., under the double reference "normal x early" or "normal x colloid." These finer distinctions are only of value for scientific accuracy.

Only glands conforming to the above anatomic description were considered as colloid in the analytical tables—the glands to which double references were made being classed in the intermediate group. There were eight cases (A-13, 25, 43, 48, 78, 80, 86, 90)—two females and six males. Relative to the state of nutrition, five were good or above and three were fair. It is significant that all cases occurred in middle-aged or old dogs. Our general impression is that in the dog sex has little or no influence on the structure of the thyroid (Fig. 3).

GROUP 3. *Glandular Hyperplasias.*—This group includes the most important thyroid changes, and it is with these changes in particular that this paper has to deal. Their greatest importance lies in the fact that they represent the primary changes[22] in the formation of all true goiters (functional hyperplasias), and hence must receive primary consideration in all inquiries into the nature of goiter. As pointed out above, there are all grades of these changes, from the normal gland to the most marked hyperplastic stage where there is scarcely any resemblance to thyroid at all. For this reason we have arbitrarily made three subgroups for analytical purposes. These groups are:

SUBGROUP 1. *Early Glandular Hyperplasias.*—This division comprises those glands which are but slightly removed from the normal. Several of the glands closely related to this subgroup are connected by double reference with the normal glands and included in the intermediate group of "normal X early." This is due to the fact that the changes are so slight that with fairness they must be considered doubly or not at all. These glands are not included in the primary analytical tables.

A typical example may be described briefly as follows: The gross appearance is nearly normal. The gland may perhaps be slightly enlarged or of a pinkish hue if compared with a normal gland. The tissue is firm to the touch and on section colloid is visible. Microscopically, the acini are small, generally circular and regular. The colloid appears normal or nearly so as to staining reaction, but after some experience one can distinguish a slight vacuolization or at least a lessened staining intensity. The epithelium is regular and of a high cubical or low columnar type. There are here and there the very beginnings of invaginations and plications of the lining epithelium. The nuclei are slightly enlarged and darkly staining, but distinctly vesicular. There is no demonstrable increase in the stroma, but the vessels, particularly the finer ramifications, appear distinctly dilated. All glands conforming to this description are considered in this subgroup (Fig. 4). In our series there were nine cases—four females and five males (A- 39, 40, 57, 62, 65, 84, 88, 92, 103). All were considered to be in the middle period of life and in all the general nutrition was good. As to breed there is nothing of importance.

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[22] Virchow, Die Krankhaften Geschülste, iii, 4 et seq.

SUBGROUP 2. *Moderate Glandular Hyperplasias.*—This division likewise offers difficulties and opportunities for error when the attempt is made to bring into a single group. Hence many closely related glands are connected by double references with either colloids or early or marked glandular hyperplasias. The reason why some are connected by double reference with colloids is that occasionally one finds glands which appear to be reverting from a marked degree of hyperplasia, but at the time of taking were histologically much like moderate hyperplasias. Only undoubted cases were, however, included in the tables for chemical analysis.

Briefly, the anatomic appearances of a typical case are: The gland is moderately enlarged, the vessels are distinctly enlarged and somewhat tortuous, the capsule is thickened and the gland tissue is moderately soft and reddish in color. There may be visible colloid. Microscopically, the colloid is reduced, vacuolated, palely staining and granular, The acini are distorted by moderate ingrowths and plications of the epithelium. The acinar epithelium is high columnar in type, regular and arranged in a single layer. The nuclei are large, round, basal and vesicular. The stroma is slightly but diffusely increased and supports a rich network of dilated and enlarged blood vessels (Fig. 5). In our series there were nine cases (A-3, 6, 21, 34, 35, 60, 70, 76, 78)—eight males and one female. It is of interest to note that only three were considered in a good state of general nutrition. As to age and breed there is again nothing of significance.

SUBGROUP 3. *Marked Glandular Hyperplasias.*—Glands in this stage of hyperplasia are more easily referred to an arbitrary subgroup for the reason that only the subgroup of moderate hyperplasias is to be differentiated, but here, too, an intermediate group is necessary.

The anatomic appearances of a typical example are as follows: The gland generally is considerably enlarged, but, as pointed out above, there may be very marked histologic changes without corresponding changes in the gross appearance. The capsule is thick and the vessels are much enlarged and tortuous. The lymphatic trunks are large, and, if exposed during life, are distended with a clear lymph-like fluid. On section the tissue is very vascular. It has a fleshy, opaque, gray-red appearance and a finely granular cut surface. There is no visible colloid. Microscopically, the stainable colloid is greatly reduced or absent, there being in its place only a small amount of pink staining granular material. The acini show extensive papillomatous ingrowths and plications of their lining epithelium, more or less effacing the acinar lumina. The epithelium is high columnar in type and arranged in a single layer. The epithelial nuclei are large, pale, round and basal. The cytoplasm is quite granular. The stroma is diffusely increased and is richly supplied with blood and lymph channels. There are also occasional collections of lymphoid cells in the stroma (Fig. 6). Only specimens conforming to the above description are considered in the analytical tables of this subgroup. In our series there are eighteen cases (A-2, 4, 10, 14, 15, 19, 23, 24, 28, 29, 41, 46, 47, 54, 67, 79, 99, 102)—ten males and eight females. As regards the state of nutrition, eight were classed as fair and ten as good. Relative to age the majority were young.

GENERAL CONSIDERATIONS OF SEX, AGE, BREED AND STATE OF NUTRITION AS AFFECTING THE STRUCTURE OF THE THYROID.

(a) *Sex.*—In this series there were forty-five females and fifty-eight males. (The remaining ten in the table were selected.) Sex does not appear to be a factor of noteworthy importance in the occurrence of thyroid changes in the dog; at least in the 103 cases included in this study no such relationship could be made out. From an experience with over 600 dogs our general impression is the same. This is quite different from the condition which obtains in man, and suggests that sexual states modify but slightly the activity of the thyroid of dogs as compared with man. Pregnancy, however, does induce hyperplasic changes similar to those occurring in man.

(b) *Age.*—Age is of more importance than is indicated in this series for the reason that practically all the cases were from adult animals. From a series of over 600 dogs we have found that puppies are much more frequently affected, and, as a rule, the hyperplasia begins before the sixth month of extrauterine life. Authors generally are agreed that youth is the most important period in the human hyperplasias as well. Age is also a notable factor in the chemistry, as will be pointed out later. Age does not bear any important relation to normal glands. Colloid glands, however, are commoner in middle aged or old dogs without relation to sex. This conforms with the view that colloid glands (goiters) are reversions from hyperplasias.

(c) *Breed* in our laboratory class of dogs is an uncertain factor. Some authors think that, clinically, goiter is commoner in spaniels, but in our experience (using the histologic standard) we are unable to ascribe any importance to breed.

(d) The state of *nutrition* seems to be a factor of considerable importance both as a cause for and as an effect of the thyroid changes. All dogs with normal, colloid or early hyperplastic glands were found to be in a condition above fair,[22] while in the moderate and marked hyperplasias thirteen out of twenty-six were below this standard. Since fat is an apparent rather than a real index of nutrition, and since it is highly probable that goiter is a nutritional disturbance, it is also probable that great exceptions or variations will be noticed by the use of such a crude index, which, however, might be rationally explained if our knowledge of nutrition were more thorough.

CHEMICAL CONSIDERATIONS; IODIN DETERMINATIONS.

(1) The *method* used in all the determinations of the amount of iodin present in the glands and tissues investigated was based on that originally described by Rabourdin[23] and extensively used by Baumann and Roos[24] in their thyroid work. The basis of the method is the fact that the amount of iodin dissolved in chloroform can be determined by the depth of the pinkish tinge which it gives to the solution. Briefly, the method consisted in incinerating the tissue in a silver dish in the presence of an alkali and potassium nitrate, and after dissolving in water the iodin was liberated by acidulating with sulphuric acid; it was then shaken out with chloroform. In another flask a known amount of iodin was added to chloroform until the tint was the same as that in the first flask.

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[22] We have used in all of our work the following terms, poor, moderate, fair, good, excellent, using as the index the visible fat noted at autopsy.

[23] Lieb. Ann., 76, S. 375.

[24] Ztschr. f. physiol. Chem., Strassb., 1896, xxi, 481.

Baumann[25] asserted that the method was not very accurate, and Oswald[26] found that amounts under 0.3 mg. of iodin could not be detected when the material was incinerated in a silver dish by this method. He substituted a nickel dish and found that from 0.1 mg. of iodin he could recover 0.08 mg., while with larger amounts the percentage of loss was much less. These workers also found that the iodin-chloroform solution soon faded, and if the determination was not made quickly the result was very inaccurate and unsatisfactory. To overcome this disadvantage Anten[27] used carbon disulphid instead of chloroform, and found that the color was much more permanent.

Our method embraces these modifications, and was carried out as follows:

The fresh tissue is weighed and is then cut into small pieces and dried to an approximately constant weight at 110 C. The dried gland is powdered and 1 gm. is taken for the iodin determination.

In a nickel evaporating dish 2 gm. of pure potassium hydroxid are dissolved in 5-10 c.c. of distilled water, and to this the 1 gm. of powdered gland is added. This is slowly evaporated to dryness, then carbonized, and on the addition of potassium nitrate the mass is reduced to a clear flux, care being taken not to add an excess of the nitrate. After cooling, the flux is dissolved in 50 c.c. of distilled water and filtered. The filter is washed with distilled water until it no longer gives a precipitate with silver nitrate. To the filtrate is added 10 c.c. carbon disulphid, 3 c.c. of 10 per cent. sulphuric acid, and 2 c.c. concentrated sulphuric acid, saturated with nitrous acid. While adding the acids the flask is well shaken, and if iodin is present the carbon disulphid takes on a reddish-violet tinge.

Into another flask saturated sodium sulphate solution is poured until it is approximately equal in amount to the liquid in the first flask. To this is added 10 c.c. carbon disulphid, 3 c.c. of 10 per cent. sulphuric acid, and 2 c.c. concentrated sulphuric acid, saturated with nitrous acid. From a burette a potassium iodid solution containing 0.1538 mg. iodin per cubic centimeter (0.20 gm. exsiccated KI to 1 L. distilled water) is run in until the color of the carbon disulphid is the same as that in the other flask. Reading off the amount of potassium iodid solution used, it is a simple matter to determine the amount of iodin in the original solution.

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25. Ztschr. f. physiol. Chem., 1896-7, xxii, 265.
26. Ztschr. f. physiol. Chem., Strassb., 1897, xxiii, 265.
27. Arch. f. exper. Path. u. Pharmakol., 1902, xlviii, 331.

The flasks used for the colorimetric method are similar to those described by Howald,[28] and have a capacity of 500 c.c. with the neck drawn out into a tube about 15 cm. long and 1.5 cm. in diameter and are glass stoppered.

Another method which was used as a control in fifteen determinations is that described by Fresenius.[29] The gland is treated exactly as has been described for the colorimetric method, and the liberated iodin is dissolved in carbon disulphid. This is then decolorized by adding from a burette a standardized solution of sodium thiosulphate, and the iodin determined by the amount of the thiosulphate solution used.

In comparing the results obtained by the two methods there occurred in one case a difference of 0.1 mg. of iodin, but, as a rule, the differences were well below this figure.

To determine whether preserved glands could be used for these determinations, parts of six glands were hardened in a 4 per cent. solution of formaldehyd in distilled water and then the iodin content was compared with that of a part of the gland treated in the usual manner. Three of the formaldehyd specimens had a slightly higher amount of iodin than the controls, but the difference between the average of those above and those below the mean was only 0.009 mg. iodin. It is, therefore, quite justifiable to use specimens preserved by formaldehyd.

(2) *Analysis of the Iodin Determinations.* Iodin determinations were made on 113 dogs' thyroids. The primary tables were made from the pure anatomic groups and subgroups, and hence include only the 67 cases there considered. This was done in the attempt to exclude all known conditions which might artificially modify the iodin content, and further, in order that the results might be taken to indicate the normal street condition. Many of the remaining 46 determinations will be utilized in the intermediate groups of Table 5 and in the analyses of the separate groups to show that the chemical conditions correspond with the anatomic relations. The remaining cases will be discussed under experimental observations.

(a) Beginning with Table 1 the following features are noted:

Excluding the colloid glands (goiters), it is found that the average amount of thyroid per kg. of body weight is practicallw the same (0.36 and 0.30 gm.) for the normals and early glandular hyperplasias, and that the moderate and marked hyperplasias show a progressive increase

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28. Ztschr. f. physiol. Chem., 1897, xxiii, 212.
29. Traité d'analyse chemique, 6th ed., p. 406.

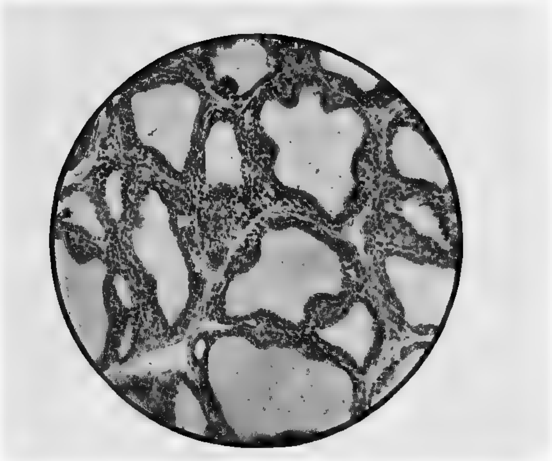

Fig. 5.—Moderate glandular hyperplasia, dog.

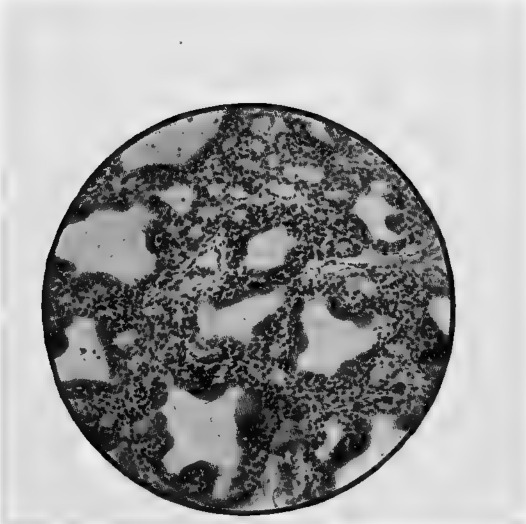

Fig. 6.—Marked glandular hyperplasia, dog.

TABLE I—Amount of Thyroid Compared with Body Weight.

Character of Gland.	Number.	Weight of Dog. Expressed in Kg.			Weight of Thyroid Expressed in gm.			Dried Thyroid Expressed in gm.			Fresh Thyroid per Kg. Body Weight. Expressed in gm.			Percentage Water in Fresh Thyroid.		
		E.*	M.	A.	E.	M.	A.	E.	M.	A.	E.	M.	A.	E.	M.	A.
Normal.........	3	6.3 4.7	5.9	5.6	3.65 1.3	1.3	2.08	0.95 0.29	0 307	0.516	0.61 0.20	0.27	0.36	78 74	77	76
Colloid.........	8	13.6 5.4	9.1	9.1	20.45 1.25	7.32	8.54	5.57 0.115	1.49	2.13	3.19 0.21	0 73	1.07	91 68	73	76
Early...........	9	15. 5.	8.2	9.3	4.5 1.3	3.	2.76	1.184 0.22	0.65	0.643	0.45 0.15	0.30	0.30	83 72	74	77
Moderate........	9	15.9 5.	8.2	8.56	22. 1.5	3.6	7.36	5.75 0.31	0.77	1.70	3.20 0.21	0.65	0.92	85 73	78	77
Marked........	18	34.5 2.5	7.2	10.	77.9 3.2	7.1	16.45	18.2 0.44	1.36	3.59	13.2 0.23	1.135	2.34	88 69	80	80

* E = extremes; M = mean; A = average.

(0.92 and 2.34 gm. respectively). The colloids are intermediate between the moderate and marked hyperplasias (1.07 gm). It is also interesting to note, as pointed out by Oswald,[30] that the hyperplasias are reduced more in weight during the process of drying, i. e., contain a larger percentage of water than either the normals or colloids.

TABLE 2.—Iodin Content of Thyroid; expressed in Milligrams.

Character of Gland.	No.	Total Iodin.			Per Kilogram of Body Weight.			Per Gram of Fresh Thyroid.			Per Gram of Dried Thyroid.		
		E	M	A	E	M	A	E	M	A	E	M	A
Normal....	3	1.891 0.984	1.384	1.419	0.32 0.156	0.294	0.256	1.064 0.512	0.757	0.777	4.772 1.990	3.205	3.322
Colloid....	8	6.675 0.415	3.013	3.232	1 236 0.069	0.359	0.402	1.039 0.132	0.406	0.459	3.608 0.846	1.816	1.985
Early....	8	0.892 0.107	0.400	0.443	0.084 0.012	0.033	0.044	0.235 0 063	0.133	0.139	1.028 0.243	0.654	0.625
Moderate...	9	1.679 0.061	0.399	0.539	0.173 0.006	0.061	0.069	0.137 0.026	0.076	0.078	0.854 0.101	0.345	0.368
Marked...	18	1.430 0.013	0.092	0.293	0.242 0.002	0.020	0.039	0.123 0.002	0.014	0.023	0.640 0.008	0.073	0.114

(b) In Table 2 the following points are brought out:

That the colloid glands (goiters) contain the most iodin—over twice as much as the normal glands—and that the hyperplasias show a decreasing amount, being least in the marked glandular hyperplasias, in spite of the fact that these glands show a progressive increase in weight, as shown in Table 1. As also noted in Table 1, the colloid glands (goiters) average more than four times the weight of the normal glands, and this accounts for the large amount of total iodin. But considering the amount of iodin per gm. of fresh thyroid, it is seen that the normal glands contain about 0.8 mg. per gm. and that there is a progressive de-

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30. Ztschr. f. physiol. Chem., 1897, xxiii, 272.

crease reaching the minimum of 0.023 mg. per gm. in the marked hyperplasias.

There being but three normal glands included in this series, it is not justifiable to consider the base line as very definitely established, but the extremes being reasonably close together, it is probably not very incorrect.

Among the colloid glands (goiters) great variations are noted in the iodin content, due possibly to the strict histologic basis of classification[31] (being irrespective of the size of the gland), and also to the possibility of the gland having just begun to undergo secondary hyperplasias (too early to be detected by any microscopic difference), in which case the iodin content is relatively low.

TABLE 3.—Percentage of Iodin.

Character of Gland.	No.	Per Body Weight.[1]			Per Fresh Thyroid.[2]			Per Dried Thyroid.[2]		
		E	M	A	E	M	A	E	M	A
Normal...	3	32 15	29	25	106 51	76	77	477 199	317	331
Colloid	8	123 7	38	41	104 13	41	46	332 84	181	195
Early	9	8 1	3	4	23 6	13	14	102 24	65	62
Moderate...	9	14 0.7	6	6	14 3	8	8	85 10	34	37
Marked.	18	24 0.2	1.5	3.8	12 0.2	1	2	64 0.8	8.5	11

1 = mgm. per kg. 2 = mgm. per gm.

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[31] That is, all glands are considered as colloids if there is any histologic evidence that they had ever undergone any degree of hyperplasia no matter how slight. This classification would, therefore, be only of scientific value for the purpose of preserving uniformity.

(c) The percentage of iodin, compared with the body weight, is about 15 per cent. greater in the colloid than in the normal glands, whereas the hyperplasias contain about 20 per cent. less than the normal glands. Here, also, there is a tendency toward a progressive diminution of iodin depending on the degree of hyperplasia. A notable exception, however, is the group of moderate glandular hyperplasias, which contain a larger percentage of iodin than the early hyperplasias, and, as before stated, this can probably be accounted for by the difficulty of determining whether a gland is reverting to a colloid—when the iodin content is higher or developing a hyperplasia from a colloid base, in which case the iodin content is lower.

The percentage of iodin per gm. of fresh thyroid shows a progressive decrease from the normal glands through the colloids to the marked glandular hyperplasias.

Comparing the percentage of iodin in the normal glands with that in the colloid glands, it is seen that in the normal glands it is less per kg. of body weight and therefore absolutely less, while per gm. of thyroid it is much greater, showing that the colloid glands possess absolutely more iodin, although they are relatively poorer.

(d) Table 4 takes into account the extremes noted in Table 2 and is so arranged that each group is divided into those above and those below the average of the preceding group. As is to be expected, partly from reasons already given, the colloid glands (goiters) show the greatest extremes, but by comparing the iodin content of the glands above with that of the glands below the average content of the group preceding (normal), it is found that 75 per cent. have a greater absolute amount of iodin, but when the iodin is calculated per gm. of fresh thyroid, 89 per cent. fall below the average preceding (normal) content. All the early hyperplasias show a decrease below the colloid averages in total iodin and in iodin per gm. of fresh thyroid.

Allusion has been made to the difficulties encountered in grouping the moderate hyperplasias. The average of the total iodin in the nine cases of moderate hyperplasia shows 56 per cent. to be below the average for the preceding (early hyperplasias) group and all to be below when the iodin is calculated per gm. of fresh thyroid. Among the marked hyperplasias 78 per cent. are below the average total iodin content of the moderate hyperplasias and 95 per cent. below when calculated per gm. of fresh thyroid.

Considering all the groups, the extremes bear out the conclusions deduced from the means (Table 2), namely: that there is a progressive decrease in the iodin content per gm. of fresh thyroid from the normal glands through the hyperplasias.

TABLE 4.—Analysis of Extremes in Iodin Content noted in Table 2.

Character of Gland.	No.		Total Iodin.			Iodin per Kg. of Body Weight.			Iodin per Gm. of Fresh Thyroid.			Iodin per Gm. of Dried Thyroid.		
			E	M	A	E	M	A	E	M	A	E	M	A
Normal. . .	3		1.891 0.984	1.384	1.419	0.320 0.156	0.294	0.256	1.064 0.512	0.757	0.777	4.772 1.990	3.205	3.322
Colloid . .	8	Above preceding Average.	6* 6.675 1.753	4.000	4.059	5 1.236 0.351	0.397	0.585	1	1.039		1	3.608	
		Below...	2* 1.091 0.415	—	0.753	3 0.128 0.069	0.093	0.097	7 0.565 0.132	0.389	0.377	7 3.261 0.846	1.599	1.755
Early. .	9	Above...		0			0			0			0	
		Below...	9 0.892 0.107	0.400	0.443	9 0.084 0.012	0.033	0.044	9 0.235 0.063	0.133	0.139	9 1.028 0.243	0.654	0.625
Moderate. .	9	Above...	4 1.679 0.608	0.796	0.969	5 0.173 0.061	0.115	0.111		0		1	0.854	
		Below...	5 0.399 0.061	0.123	0.195	4 0.039 0.006	0.013	0.018	9 0.137 0.026	0.076	0.078	8 0.519 0.101	0.318	0.308
Marked . .	18	Above...	4 1.430 0.615	0.818	0.920	3 0.242 0.091	0.135	0.156	1	0.123		1	0.640	
		Below...	14 0.473 0.013	0.080	0.114	15 0.035 0.002	0.014	0.016	17 0.042 0.002	0.014	0.016	17 0.184 0.008	0.069	0.083

* Figures indicate the number of glands.

TABLE 5.—Average Iodin Content of Pure and Intermediate Groups, Arranged in Anatomic Order.

Character of Glands.	No. of Cases.	Iodin per kg. of Body Weight.	Iodin per gm. of Fresh Thyroid.	Iodin per gm. of Dried Thyroid.	Fresh Thyroid per kg. of Body Weight.
Normals (pure)	3	0.256	0.777	3.322	0.27
Normals X colloids (intermediate)	1	0.218	0.480	2.480	0.46
Normals X early (intermediate)	7	0.054	0.173	0.881	0.27
Colloids (pure)	8	0.402	0.459	1.985	0.73
Colloid X early (intermediate)	4	0.181	0.217	0.914	0.79
Early (pure)	9	0.044	0.139	0.624	0.30
Early X moderate (intermediate	1	?	0.082	0.262	?
Moderate (pure)	9	0.069	0.078	0.368	0.65
Moderate X marked (intermediate)	9	0.096	0.055	0.283	1.52
Marked (pure)	...	0.039	0.023	0.114	1.14

(e) This table includes, besides the cases belonging to the pure histologic groups, those which are intermediate or which possess characters common to two groups, and excludes all cases which are complicated with neoplasm, hemorrhage, cystic changes, etc., and those operated upon or having received iodin in the laboratory or elsewhere.

It is compiled from averages only, and shows that the intermediate groups have iodin contents which fall between the iodin contents of the groups to which they are connected by double references. This table accentuates the fact brought out in Table 2 that the iodin per gm. of thyroid shows a progressive decrease from the normal glands through colloids to the hyperplasias, including the intermediate cases with double references.

(f) *Analyses of the individual cases of separate groups.* It will be noted that the extremes in the iodin content within the separate groups show such marked differences that it seemed unsafe to base conclusions solely on the averages. We compared, therefore, the iodin content with the anatomic changes of the individual members of each group.

Normal Glands.—The normal glands do not show very marked extremes, but as but three glands were considered, it is possible that a larger number might have shown greater variations. It is of interest, however, to note that in these cases the amount of iodin per gm. of thyroid varied inversely with the amount of iodin per kg. of body weight. An explanation of this fact might be that while the normal glands tend to a more or less constant amount of iodin per gm. of thyroid this constancy is not absolute, and when there is a greater quantity of thyroid tissue in one case the percentage of iodin will be less than in another case having less thyroid tissue.

As will be shown in the other groups, there seem to be comparatively wide limits in the iodin content between which there are no demonstrable histologic changes. On the other hand, there seems to be a fairly definite minimal amount of iodin per gm. of thyroid necessary for the maintenance of the normal histological appearance of the epithelium. If the iodin content falls below this minimal amount, hyperplastic changes in the gland follow. This minimal iodin content per gm. of thyroid is practically the same for the colloid and the normal glands as is shown in Table 5. In this table it is seen that hyperplastic changes have started when the iodin content falls below 0.173 mg. per gm. of fresh thyroid in the normal glands and to 0.217 mg. in the colloid glands.

Colloid Glands (*goiters*).—In the glands comprising this group there is, in general, an increase in the amount of iodin per gm. of thyroid associated with flattening of the epithelial cells and a decrease in the iodin in those glands having more cubical epithelial cells. As regards the relation between the amount of thyroid per kg. of body weight and the histologic changes—the smaller glands show evidence of epithelial activity (hyperplasia), while the larger glands show no such activity (cells very flat cubical).

Examining the cases further, it is found that six of the eight glands show that the increase in the amount of iodin per gm. of thyroid is coincident with a decrease in the amount of thyroid per kg. of body weight; in other words, the percentage of iodin is inversely proportional to the amount of thyroid, but since the amount of thyroid is very greatly increased, the total amount of iodin is also much increased, notwithstanding the fact that the colloid is relatively poorer in iodin than is normal colloid. This inverse proportion of iodin to the amount of thyroid agrees with that already noted in the normal glands, and our explanation is the same.

We have already pointed out that the colloid gland is as nearly normal as a gland can become after once having undergone a hyperplastic change, and it is of particular interest that the chemical findings should sustain this opinion which was based primarily on the histology, but which is now supplemented by the biologic facts that partial removal of colloids is followed by compensatory hyperplasia of the remaining portion, and also, as shown by Baumann[32] for the normal glands, that compensatory hypertrophy occurs when iodin is restricted in the diet.

Oswald[33] has shown that in man and calves the iodin content in general varies with the amount of colloid in the gland, and also that in colloid goiters the percentage of iodin is decreased as compared with normal colloid. Our results with dog's colloid goiters agree with his findings.

Analyzing the glands still further, it is seen that, notwithstanding the comparatively low percentage of iodin in the colloid glands, the amount is always larger than that in colloids beginning to undergo hyperplasia. It seems probable that before a glandular hyperplasia can revert to a colloid, a necessary minimal amount of iodin must be present. Further, that reversion having once begun, the colloid accumulates more rapidly than iodin can be accumulated in the colloid (in the presence of a limited supply of iodin) without interfering with the physiologic requirements of the body at large, and, therefore, we have a colloid which is relatively poor in iodin as compared with normal colloid, although the absolute amount of iodin in the whole gland may be and is much greater than in a normal gland, and is, if our interpretation be correct, necessarily greater than the normal physiologic needs of the organism. But in the presence of a large excess of iodin the colloid of a reverting hyperplastic gland is capable of assimilating as much iodin as normal colloid. In other words, a certain amount of iodin is necessary before reversion can occur at all. If this supply of iodin be only slightly in excess of the physiologic needs, then the large amount of colloid which is formed will be relatively poor in iodin, although the total iodin in the gland may be and is actually greater than that present in a normal gland. If, on the other hand, the gland reverts in the presence of a larger excess of iodin, the colloid which is formed will be rich in iodin, approaching or equalling the iodin content of the colloid of normal glands.

"Colloid X Early" Glandular Hyperplasia.—This group shows that the amount of colloid in the gland decreases as the amount of iodin increases; that the colloid decreases as the gland becomes smaller, and that the iodin per gm. of fresh thyroid decreases as the gland becomes larger. These conclusions hold good for three out of four glands—the fourth gland was reverting from a marked hyperplasia, while the others were in the early stage of secondary hyperplasia engrafted on colloid bases.

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[32] Ztschr. f. physiol. Chem., 1896-7, xxii, 14.

[33] Ztschr. f. physiol. Chem., 1897, xxiii, 265.

"Normal X Early" Glandular Hyperplasia.—In this group, roughly speaking, the amount of iodin per gm. of fresh thyroid decreases as the amount of thyroid per kg. of body weight increases. Moreover, the amount of colloid decreases as the amount of thyroid per kg. of body weight increases, and, finally, in two-thirds of the glands the amount of iodin decreases as the colloid decreases. Altogether the results are neither striking nor conclusive.

Early Glandular Hyperplasias.—The amount of iodin per gm. of fresh thyroid decreases as the amount of thyroid per kg. of body weight increases. There is no apparent relation between the amount of iodin and the amount of colloid present in the gland, nor does the degree of hyperplasia bear any marked relationship to any of the other factors. The amount of thyroid per kg. of body weight varies inversely with the amount of colloid in a fairly constant manner—the only striking exception—A-103—approaches histologically the next group.

Moderate Glandular Hyperplasias.—With the exception of three glands, the amount of iodin per gm. of fresh thyroid varies directly with the amount of thyroid per kg. of body weight. Two of the three exceptions have such an unusually large amount of thyroid per kg. of body weight that they suggest some other pathological changes. Roughly speaking, the amount of iodin increases as the amount of colloid increases. No relation seems to exist between the amount of colloid and the amount of thyroid per kg. of body weight. The epithelial differences are not sufficiently characteristic to permit drawing any conclusions.

"Moderate X Marked" Glandular Hyperplasia.—In seven out of the nine glands the iodin tends to vary inversely with the amount of thyroid per kg. of body weight. Also the colloid tends to vary inversely between the amount of colloid and the amount of thyroid per kg. of body weight.

Marked Glandular Hyperplasias.—In general the amount of thyroid per kg. of body weight tends to vary inversely with the amount of iodin, but to this there are some exceptions. There seems to be no relation between the iodin content and the amount of colloid, though the amount of visible colloid is so small that accurate estimations are impossible. The amount of colloid tends to run parallel with the amount of thyroid per kg. of body weight, but with rather numerous exceptions.

Summary of the Relation of the Iodin Content, Size of Thyroid, and Quantity of Colloid.

In Table 6 the amount of iodin is found to vary inversely with the amount of thyroid per kg. of body weight, and the amount of iodin in the colloid varies inversely in the normal and colloid glands. In the

TABLE 6.—A. Based on the Averages from Table 5.

Character of Glands.	Iodin to Thyroid per kg. of Body Weight.	Iodin to Colloid.	Colloid to Thyroid per kg. of Body Weight.
(1) Normals and colloids	Inverse	Inverse	Direct
(2) From normals through hyperplasias	Inverse	Direct.	Inverse

B. Based on the analyses of the individual glands of the separate groups and intermediates, as described in the preceding section.

Character of Glands.	Iodin to Thyroid per kg. of Body Weight.	Iodin to Colloid.	Colloid to Thyroid per kg. of Body Weight.
(1) Normals	Inverse	Inverse	Direct
(2) Colloids	Inverse	Inverse	Direct
(3) Normal X early	Inverse	Direct	Inverse
(4) Early	Inverse	No relation	Inverse
(5) Moderate	Direct (?)	Direct	No relation
(6) Moderate X marked	Inverse	Inverse (?)	No relation
(7) Marked	Inverse	No relation	Direct

hyperplasias the amount of iodin also varies inversely with the amount of thyroid per kg. of body weight, but the amount of iodin in the colloid varies directly with the colloid. In the normal glands and in the colloids the amount of colloid in 1 gm. of fresh thyroid compared with the amount of thyroid per body weight seems to vary directly, while in the hyperplasias it varies inversely.

Comparing these conclusions with those of the analyses of the individual glands of the separate groups, a general agreement is found; that is, these changes are evident not only when whole groups are compared, but when the gradations of the individual members of the groups are compared. The agreement is not, however, absolute in detail. From Table 6-B it will be seen that the results in the separate groups agree with those of the averages in eight instances and are contrary in three. Similarly, within each group, individual exceptions are noted. It appears evident, therefore, that other factors than iodin are concerned which are not taken into account in our observations. In some of the cases at least the factors were plainly accidental, such as hemorrhage, cysts, etc.

However, the very striking fact that the same general laws hold good for the individual cases as well as for the whole group proves that iodin is the predominant objective factor.

(3) *Effects of Weight, Age, Sex, Nutrition and Breed on the Iodin Content.*—(a). The amount of normal thyroid per kg. of body weight is about 0.35 gm., while in our groups it averaged 1.07 for the colloids, 0.30 gm. for the early glandulars, 0.92 gm. for the moderates, and 2.34 for the marked glandular hyperplasias.

(b) Age in relation to iodin content. Thirteen of the sixty-seven glands used in the tables were from dogs under 6 months of age, and show a distinctly low percentage of iodin. In this connection it might be recalled that Baumann found that children at birth rarely had any iodin in the thyroids and that with years the quantity progressively increased, being greatest between the ages of 25 and 45 and diminishing again in old age. Six glands in our series were marked "old," but show no definite change.

(4) Nutrition is probably of more importance than is here indicated, since practically all dogs were in good health. As a rule, the very marked cases of glandular hyperplasia occur in the young and are associated with a greatly reduced iodin content or none at all.

(5) Breed is an indeterminable factor in our cases.

(6) Intercurrent factors. Two pregnant bitches were included in our series; these showed no definite change in iodin content.

EXPERIMENTAL OBSERVATIONS.

(1) *Effect of Feeding Iodin Containing Substances* (Table 7).—In the six cases one lobe was removed as a control, and then different iodin-containing substances were administered in known quantities to ascertain the rapidity of assimilation and the amount stored, as well as to determine what changes occurred in the histologic structure of the gland and the rapidity of these changes. The iodin was administered in the following forms: Saturated alcoholic solution of iodin; syrup of the iodid of iron; desiccated thyroids (commercial); fresh sheep thyroids (all degrees of glandular hyperplasia); full mixed diet (constant factor in all).

As regards the changes in the size of the gland, all the hyperplastic glands show a remarkable reduction in the weight of the remaining lobe, which conforms with the vast clinical observations on man and animals; and, within limits, this occurs without apparent relation to the forms in which the iodin is administered. On the other hand, the normal and colloid glands show no diminution in size.

TABLE 7.—Experimental — Iodin Feeding.

No. of Dog.	Weight of Dog. Kg.	Weight of Fresh Thyroid.	Weight of Dried Thyroid.	Character of Gland.	†Total Iodin.	Iodin per Kg. of Body Weight.	Iodin per Gm. of Fresh Thyroid.	Iodin per Gm. of Dried Thyroid.	Remarks.
26a	2.4	0.24	0.04	Normal . .	0.092	0.038	0.380	2.3	15 gtt. sat. alc. sol. iodin in 13 days; 27 days before death.
26b	4.0	0.305	0.06	Normal .	0.215	0.053	0.705	3.467	
51a	3.2	22.1	4.47	Colloid. . .	3.16	0.987	0.138	0.707	6 5-gr. thyroid tablets in 3 days; 2 days before death.
51b	3.0	23.1	5.85	Colloid. . .	5.669	1.889	0.245	0.969	
16a	5.0	4.15	0.714	Moderate .	0.061	0.012	0.014	0.086	65 5-gr- thyroid tablets in 13 days; 14 days before death.
16b	3.2	2.7	0.61	Colloid, . .	1.061	0.331	0.393	1.739	
18a	5.4	7.5	1.63	Moderate .	0.425	0.076	0.056	0.261	545 gms. fresh sheep thyroid in 10 days; 8 days before death.
18b	3.18	4.75	1.25	Colloid. . .	6.018	1.889	1.265	4.184	
52a	2.7	3.6	0.52	*Moderate Marked	0.215	0.079	0.057	0.412	15 gtt. sat. alc. sol. iodin in 3 weeks; 2 days before death.
52b	2.8	2.0	0.51	Colloid. .	1.63	0.563	0.815	3.196	
55a	7.27	72.0	13.15	*Moderate Marked.	0.61	0.083	0.008	0.054	7 gtt. sat. alc. sol. iodin in 7 days; 1 day before death; died suddenly; embolus.
55b	6.36	57.2	11.97	Moderate .	16.746	2.633	0.292	1.399	

* Moderate marked glandular hyperplasia.

† Iodin is expressed in milligrams.

The histologic changes in all the hyperplastic glands show a return to the colloid type. In our experience this reversion takes place in about two or three weeks, when there is an excess of iodin present. None of the cases, including the normal glands, show any hyperplasic changes even though the period of forty days, which Halsted advised to allow for the occurrence of hyperplasia, was permitted to elapse.

The total iodin in the control thyroid was invariably much less than the total iodin in the lobe removed after feeding iodin. The amount of iodin assimilated does not seem to be so much dependent on the form in which it is administered as on the amount of glandular tissue present.

It is interesting to note that the iodin content of the colloid of normal glands can be much increased, and also that the colloid from colloid goiters can have its iodin content increased to the same extent. In one dog (A-17), not included in the table, one thyroid lobe was removed during pregnancy. It weighed 0.7 gm. and histologically showed early hyperplasia. The remaining lobe was removed at the end of pregnancy, the dog having received 0.2 gm. of iodin. The lobe weighed 0.65 gm., and histologically was a pure colloid. The iodin in this gland per gm.

TABLE 8.—Experimental—Without Iodin Feeding.

No. of Dog.	Weight of Dog.	Weight of Fresh Thyroid.	Weight of Dried Thyroid.	Character of Gland.	Total mg. Iodin.	Iodin per Kg. of Body Weight.	Iodin per Gm. of Fresh Thyroid.	Iodin per Gm. of Dried Thyroid.
27a	1.85	0.25	0.07	Normal.	0.062	0.033	0.248	0.886
27b	1.53	0.15	0.025	Early.	0.038	0.024	0.253	1.520
63a	12.7	14.25	3.41	Colloid.	4.249	0.334	0.298	1.246
63b	12.7	14.0	4.03	Colloid.	1.302	0.102	0.092	0.323
95a	5.9	5.1	1.2	Colloid.	1.284	0.218	0.251	1.076
95b	5.67	3.4	0.77	Colloid.	0.554	0.097	0.163	0.719
64a	2.7	2.25	0.36	Early.	0.108	0.005	0.051	0.300
64b	4.1	2.3	0.41	Colloid.	0.954	0.332	0.415	2.326
94a	2.15	1.5	0.28	Early.	0.184	0.085	0.122	0.657
94b	1.95	1.0	0.21	Early.	0.215	0.110	0.215	1.024
74a	5.44	3.6	0.5	Moderate.	0.261	0.048	0.072	0.521
74b	6.35	2.8	0.55	Early.	0.799	0.125	0.275	1.452

was 1.093 mg., which is above the average for a normal gland. Specimens of liver and muscle showed no trace of iodin.

(2) *Effect of Removing One Lobe Without Administration of Iodin* (Table 8).—In the six dogs one lobe was removed as a control, and the dogs were then kept on the usual laboratory diet (bread, cooked meat, salt and water) without the direct administration of iodin. All show reduction in the size of the remaining lobe, manifested most particularly in the hyperplasic glands, but not as great as is noted in the dogs which had received iodin. The colloids also show some reduction in size, but to a less extent.

Dog 27a was used as the control for 26a. They were sisters and both had normal control lobes. The second lobe of 27a showed the usual compensatory hypertrophy (Halsted), while the second lobe of 26a remained normal in type, though it grew somewhat in size.

The colloid glands showed no histologic evidence of hypertrophy, although chemically they did show evidence (i. e., a reduction in the iodin content). All the hyperplasic glands showed some evidence of reversion, but it was very slight compared with that occurring in the dogs which had been fed iodin. The normal and colloid glands both fell off rapidly in their iodin content, in sharp contrast to those fed iodin. On the other hand, however, the hyperplasic glands showed a slight increase in the iodin content, though much less than in those where iodin had been fed.

This suggests that keeping the dogs on the same diet, the hyperplasic (hyperactive) glands are more capable of taking up iodin than are the more inactive normal or colloid glands.

When we consider dogs 26 and 27 along with dogs 7, 9 and 11, and in connection with the general experimental evidence thus far obtained from various investigators, it further suggests that there is a minimal normal amount of thyroid tissue and a minimal normal amount of secretion necessary for the normal body economy, which is dependent on the available supply of iodin, i. e., the greater the supply of iodin the less the necessary amount of thyroid. This suggestion is further supported by the fact, first pointed out by Halsted, that it is possible to produce goitrous pups by the partial removal of the mother's thyroid, when she is kept on the ordinary diet. We have in addition, experimentally shown[34] that this can not occur in the presence of full amounts of iodin.

OBSERVATIONS ON THE IODIN CONTENT OF THE THYROID GLANDS OF OTHER ANIMALS.

Since it has been shown by many observers that in goitrous districts all mammals are, to a greater or lesser extent, prone to thyroid changes, it is proper that tables be made both of their anatomic changes and their iodin contents in order that the physiologic importance of iodin can be estimated. Though we have merely begun this task, the results may be hinted at and suggestions made.

Human Examinations. — Of two cases anatomically classified as "colloid X early," glandular hyperplasia, one was clinically normal and contained 0.208 mg. of iodin per gm. of fresh thyroid, while the other case was an old colloid goiter on which was engrafted an early hyperplasia. This case was clinically regarded as early exophthalmic goiter engrafted on an old colloid goiter. The gland contained 0.162 mg. iodin per gm. of fresh thyroid. In these two cases the anatomic changes and their iodin contents agree and are similar to the findings in dogs. Of four other cases clinically regarded as exophthalmic goiter (mild cases), who had, however, been treated with iodin, all were anatomically pure colloid goiters and showed iodin contents of 0.304, 0.633, 0.707, 0.883 mg. respectively, thus agreeing with the observations of the others on the rapid storage of iodin, and also agreeing with our anatomic observations indicating that there is a return to the colloid type on the admin-

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[34] Cleveland Med. Jour., February, 1908, vii. 105.

TABLE 9.—TO ACCOMPANY ARTICLE BY DAVID MARINE, M.D., AND W. W. WILLIAMS, M.D., ON RELATION OF IODIN TO THE STRUCTURE OF THE THYROID GLAND.

No. of Dog and Sex.	Weight *	Breed and Age.	Macroscopic.				Microscopic.					Chemic.							Remarks.
									Glandular Hyperplasia.										
			Nutrition.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Early.	Moderate.	Marked.	Weight fresh thyroid.	Weight dried thyroid.	Percent. water.	Total iodin.	Iodin per kg. body weight.	Iodin per gm. fresh thyroid.	Iodin per gm. dried thyroid.	
A-1....M.	3.63	Collie. Young	Good	Yellow-pink, translucent.	Firm	Normal	+?	..	+	..	..	1.0	0.2	80	0.185	0.051	0.018	0.927	
A-2....M.	9.09	Spaniel. Middle	Fair	Gray, fleshy	Soft	None	..	..	..	..	+	59.0	18.3	69	0.837	0.091	0.014	0.046	Moderate hemorrhagic-cystic change.
A-3....M.	6.36	Collie. Middle.	Fair	Pink, opaque	Moderate	Reduced	..	..	..	+	..	1.5	0.31	79	0.070	0.011	0.047	0.227	
A-4....M.	8.2	Terrier. Middle	Fair	Gray-pink, fleshy	Soft	None	..	..	..	..	+	7.0	1.46	79	0.269	0.032	0.038	0.184	
A-5....M.	11.81	Fox terrier. Middle	Excellent	Pink	Moderate	Reduced	..	..	..	+	..	*1.9	0.36	81	0.123	0.104	0.045	0.171	*Right lobe removed 1 year ago. Iodir for 2 lobes.
A-6....M.	8.2	Terrier. Middle	Moderate	Yellow-pink	Firm	Reduced	..	..	..	+	..	1.7	0.36	79	0.123	0.015	0.072	0.345	
A-7....M.	15.9	Scotch terrier. Middle	Excellent	translucent	Firm	Normal	..	+	..	..	..	*3.85	1.13	70	3.146	0.198	0.812	2.784	*Right lobe removed 1 year ago. Wei 5 gm. Iodin—absolute amount.
A-8...F.	10.0	Bull terrier. Middle	Excellent	translucent	Firm	Abundant	..	+	..	..	..	54.9	16.9	69	26.769	2.679	0.487	1.584	Uterus and ovaries removed 6 month
A-9....M.	9.98	Scotch terrier. One year.	Excellent	leshy	Moderate	None	..	..	..	..	+	*1.05	0.23	78	0.031	0.003	0.029	0.135	* Right lobe removed 7 months ago. I amount.
A-10....M.	5.9	Terrier. Young	Fair	leshy	Soft	None	..	..	..	..	+	77.9	15.1	80	1.430	0.242	0.018	0.090	
A-11....M.	8.4	Fox terrier. Middle	Excellent	translucent	Firm	Abundant	..	+	..	..	..	*4.55	1.35	70	2.087	0.248	0.458	1.538	*Right lobe removed 1 year ago. Wei odin—absolute amount.
A-12....M.	20.86	Bulldog. Young adult	Good	red	Soft	None	..	..	..	..	+	39.35	7.32	81	2.701	0.129	0.068	0.369	Desquamation—not included in tables
A-13....M.	9.10	Terrier. Middle	Fair	red, translucent	Moderate	Normal	..	+	..	..	..	20.45	5.57	73	5.224	0.574	0.255	0.938	
A-14...F	9.5	Cur. Middle	Fair	nk, vascular	Soft	None	..	..	..	..	+	4.75	0.70	85	0.092	0.014	0.019	0.132	
A-15....M.	13.60	Collie. Middle	Good	nk, fleshy	Soft	None	..	..	..	..	+	3.20	0.54	83	0.062	0.005	0.019	0.114	
A-16a...M.	5.0	Terrier. Old	Fair	nk, fleshy	Soft	None	..	..	..	+	+?	*4.15	0.714	82	0.061	0.012	0.014	0.086	*Left lobe removed, Jan. 22, 1907. Fe thyroid (commercial).
A-16b...M.	3.2	Terrier. Old	Emaciated	translucent	Firm	Normal	..	+	+?	..	..	*2.70	0.61	77	1.061	0.331	0.393	1.739	*Died Feb. 20, 1907. Sixty-five 5-gr. ta 28 days.
A-17a...F.	5.4	Dachshund. Middle	Good	ellow, translucent.	Firm	Normal	+	..	+	..	..	0.70	0.192	72	......	......	......	......	Iodin not determined—accident. Pr lobe removed, Feb. 20, 1907.
A-17b...F.	5.0	Dachshund. Middle	Good	ellow	Firm	Normal	..	+	..	..	..	0.65	0.135	79	0.623	0.124	1.093	4.615	Killed March 15, 1907, 33 days after bi ; 200 mg. iodin given. Bits of liver and muscle sh of iodin.
A-17c...F.	0.210	Daughter of A-17b; 3 days.	Good			Normal	+	..	..	..	..	0.01	0.002	80	......	......	......	......	Slightest possible trace of iodin.
A-18a...F.	*5.4	Terrier. Middle	Fair	nk, fleshy	Soft	None	..	..	..	+	..	*7.5	1.63	78	0.425	0.076	0.056	0.261	* Left lobe removed Jan. 22, 1907. Dog ep thyroids.
A-18b...F.	3.18	Terrier. Middle	Emaciated	ellow, translucent.	Firm	Abundant	..	+	..	..	..	*4.75	1.25	83	6.018	1.889	1.265	4.184	*Died Feb. 11, 1907. Had taken 545 heep thyroids (hyperplasias).
A-19....F.	2.5	Terrier. Middle	Poor	leshy	Soft	None	..	..	..	..	+	12.22	2.35	81	0.073	0.029	0.006	0.031	
A-20....M.	5.6	Bull terrier. Pup	Excellent	translucent	Firm	Abundant	..	+	..	..	..	*27.0	6.95	73	15.429	2.721	0.285	1.110	*Right lobe removed. Fed iodin. Cre odin calculated as for 2 lobes.
A-21....M.	9.0	Hound. Middle	Fair	Pink, fleshy	Moderate	Reduced	..	..	..	+	..	2.3	0.6	74	0.061	0.006	0.026	0.101	
A-22....F.	?	?	?	Yellow-pink	Firm	Reduced	..	..	+	+	..	5.1	1.63	68	0.425	?	0.082	0.261	
A-23....F.	4.5	Terrier. Old	Fair	Pink	Moderate	None	..	..	..	..	+	5.0	0.96	81	0.615	0.135	0.123	0.640	
A-24....M.	15.9	Spaniel. Middle	Fair	Pink, fleshy	Soft	None	..	..	..	..	+	7.2	1.4	80	0.084	0.005	0.012	0.061	
A-25....M.	11.3	Hound. Middle	Fair	Yellow, pink	Firm	Normal	..	+	..	..	..	8.6	2.27	74	4.676	0.351	0.543	2.060	A reverted glandular hyperplasia (spontaneous).
A-26a...F.	2.4	Terrier. Pup	Fair	Yellow, pink	Firm	Reduced	+	..	..	..	..	*0.24	0.04	83	0.092	0.038	0.380	2.30	*Right lobe removed Feb. 15, 1907. Fed 15 gtt. sat. als. sol. iodin.
A-26b...F.	4.0	Terrier. Pup	Excellent	Clear, yellow, translucent.	Firm	Normal	+	..	..	..	..	*0.305	0.06	80	0.215	0.053	0.705	3.467	*Killed April 2, 1907. Had grown rapidly. Muscle—slightest trace iodin.
A-27a...F.	1.85	Terrier. Pup	Fair	Yellow-pink	Firm	Reduced	+	..	..	..	..	*0.25	0.07	72	0.062	0.033	0.248	0.886	*Right lobe removed Feb. 15, 1907. No iodin administered.
A-27b...F.	1.53	Terrier. Pup	Emaciated	Yellow-pink	Firm	Reduced	..	..	+	..	..	*0.15	0.025	83	0.038	0.024	0.253	1.52	*Died April 2, 1907. Pneumonia. Iodin—slightest possible trace in muscle.
A-28....M.	11.3	Terrier. Middle	Good	Pink, fleshy	Soft	None	..	..	..	..	+	8.4	1.54	82	0.035	0.003	0.004	0.023	
A-29....M.	5.4	Collie. Pup	Good	Red, fleshy	Soft	None	..	..	..	..	+	4.8	0.44	88	0.031	0.006	0.006	0.069	
A-30....F.	14.5	Bull. Middle	Fair	Yellow-pink	Moderate	Reduced	..	+	..	+	..	8.25	1.98	76	2.423	0.167	0.293	1.224	Beginning reversion.
A-31....F.	9.07	Collie. Pup	Good	Yellow, translucent	Firm	Normal	+	..	+	..	..	2.2	0.487	77	0.631	0.069	0.286	1.296	
A-32....M.	5.9	Beagle. Young	Poor	Gray-pink	Moderate	Reduced	..	+	..	+	+	29.8	7.24	75	0.449	0.076	0.015	0.062	Probably marked glandular.
A-33....M.	8.16	Terrier. Young	Good	Pink, fleshy	Moderate	Reduced	..	+	..	+	..	25.0	5.75	77	1.771	0.216	0.071	0.308	Reverting, spontaneously.
A-34....M.	5.6	Terrier. Middle	Fair	Red-yellow	Moderate	Reduced	..	..	..	+	..	4.9	0.72	85	0.615	0.173	0.125	0.854	
A-35....M.	11.8	Spaniel. Middle	Good	Red-opaque	Soft	Reduced	..	..	..	+	..	22.0	5.75	74	1.679	0.142	0.076	0.292	
A-36....M.	10.0	Terrier. Middle	Good	Yellow-pink	Moderate	Reduced	..	+	..	+	..	7.0	2.08	70	1.823	0.183	0.262	0.784	Reverting, spontaneously.
A-37....M.	11.0	Hound. Middle	Poor	Pink-opaque	Moderate	Reduced	..	..	..	+	+	40.0	11.06	72	4.015	0.365	0.100	0.363	
A-38....M.	6.3	Bull terrier. Pup	Excellent	Clear, yellow, translucent	Firm	Normal	+	..	..	..	..	1.3	0.31	77	0.984	0.156	0.757	3.205	
A-39....F.	6.3	Terrier. Middle	Fair	Gray, translucent	Firm	Normal	..	..	+	..	..	1.7	0.44	74	0.108	0.017	0.063	0.243	
A-40....M.	14.0	Setter. Middle	Good	Yellow-pink	Firm	Reduced	..	..	+	..	..	4.5	1.184	74	0.890	0.062	0.197	0.752	
A-41....F.	5.0	Terrier. Pup	Poor	Fleshy-pink	Soft	None	..	..	..	..	+	5.8	0.87	85	0.046	0.009	0.008	0.053	
A-42....M.	12.7	Pointer. Middle	Good	Yellow-pink	Firm	Normal	+	..	+	..	..	6.5	1.56	76	1.271	0.100	0.195	0.815	
A-43....F.	6.0	Terrier. Middle	Good	Clear, yellow, translucent	Firm	Normal	..	+	..	..	..	1.25	0.115	91	0.415	0.039	0.332	3.608	
A-44a...F.	7.7	Hound. Six months	Poor	Red, gray	Moderate	Reduced	..	..	..	+	+	*40.0	8.3	79	1.021	0.132	0.025	0.123	*Right lobe removed March 14, 1907. Gland hemorrhagic.
A-44b...F.	7.7	Hound. Six months	Poor	Red, gray	Moderate	Reduced	..	..	..	+	+	*25.0	3.74	85	0.288	0.037	0.011	0.077	*Died, wound infection after 2 days. Half left lobe used for iodin, absolute amount.
A-45a...M.	6.3	Terrier. Middle	Good	Pink, opaque	Soft	None	..	..	..	..	+	*4.0	0.75	81	0.015	0.002	0.004	0.020	*Right lobe removed, March 14, 1907.
A-45b...M.	6.3	Terrier. Middle	Good	Pink, opaque	Soft	None	..	..	..	..	+	*1.1	0.24	78	0.015	0.002	0.013	0.062	*Killed, infected, March 16, 1907. Half + l. lobe used for iodin—absolute amount.
A-46....M.	10.4	Bull. Middle	Good	Gray, translucent	Firm	None	..	..	..	..	+	3.35	0.685	80	0.092	0.008	0.027	0.184	
A-47....F.	6.3	Spaniel. Young	Good	Pink, opaque	Moderate	None	..	..	..	..	+	8.0	1.58	80	0.013	0.002	0.002	0.008	
A-48....M.	13.6	Terrier. Middle	Good	Clear, yellow, translucent	Firm	Normal	..	+	..	..	..	3.1	0.86	72	1.753	0.128	0.565	2.033	Considered colloid, using strict classification.
A-49....F.	5.4	Cur. Middle	Fair	Pink, translucent	Firm	Normal	+	..	+	..	..	1.7	0.54	68	0.261	0.048	0.153	0.483	
A-50....F.	17.0	Bull. Middle	Good	Pink, translucent	Firm	Reduced	..	+	+	..	..	16.1	4.69	70	2.021	0.119	0.125	0.431	Spontaneous reversion.
A-51a...M.	3.2	Terrier. Middle	Fair	Pink, translucent	Moderate	Reduced	..	+	..	..	..	*22.1	4.47	79	3.160	0.987	0.138	0.707	*Left lobe removed March 29, 1907. Fed desiccated thyroids (commercial).
A-51b...M.	3.0	Terrier. Middle	Emaciated	Pink, translucent	Moderate	Normal	..	+	..	..	..	*23.1	5.85	74	5.669	1.889	0.245	0.969	*Died April 4, 1907. Pneumonia. Received 6 tablets, each 5 grains.
A-52a...F.	2.7	Terrier. Pup	Fair	Pink, opaque	Soft	None	..	..	..	+	+	*3.6	0.52	85	0.215	0.079	0.057	0.413	*Right lobe removed March 29, 1907. Fed iodin, 10 gtt. sat. alc. sol.
A-52b...F.	2.8	Terrier. Pup	Good	Clear, yellow	Firm	Normal	..	+	..	..	..	*2.0	0.51	74	1.630	0.563	0.815	3.196	*Killed April 23, 1907.
A-53....F.	9.0	Spaniel. Middle	Good	Gray-pink	Moderate	Reduced	..	+	..	+	..	6.9	1.55	77	0.547	0.060	0.079	0.353	
A-54....M.	5.4	Terrier. Middle	Good	Red, opaque	Soft	None	..	..	..	..	+	21.1	3.38	84	0.155	0.028	0.028	0.046	
A-55a...M.	7.27	Bull. Pup	Poor	Purple, opaque	Soft	None	..	..	..	+	+	*72.0	13.15	82	0.610	0.083	0.008	0.054	*Left lobe removed April 1, 1907. Cretinoid dog.
A-55b...M.	6.36	Bull. Pup	Poor	Pink, opaque	Soft	None	..	..	..	+	..	*57.2	11.97	78	16.746	2.633	0.292	1.399	*Killed April 8, 1907. Fed iodin, 7 gtt. sat. alc. sol.
A-56....F.	7.3	Spaniel. Middle	Good	Clear, yellow	Firm	Normal	+	..	+	..	..	1.5	0.38	74	0.477	0.065	0.318	1.255	
A-57....F.	6.8	Collie. Middle	Fair	Pink-yellow	Firm	Normal	..	..	+	..	..	3.1	0.87	72	0.569	0.084	0.183	0.654	Scabies.
A-58....F.	5.0	Terrier. Young	Poor	Pink, opaque	Moderate	Reduced	..	+	..	+	..	5.82	1.34	76	0.762	0.152	0.131	0.569	
A-59....F.	11.0	Collie. Old	Good	Pink translucent	Moderate	Reduced	..	+	..	+	..	4.29	1.007	76	0.634	0.058	0.148	0.631	
A-60....F.	5.3	Terrier. Young	Good	Pink, opaque	Soft	Reduced	..	..	..	+	..	16.97	3.6	79	0.608	0.115	0.035	0.169	
A-61....F.	4.9	Terrier. Young	Good	Pink, opaque	Soft	Reduced	..	..	..	+	+	5.09	0.8	84	0.185	0.037	0.036	0.231	
A-62....M.	7.3	Terrier. Middle	Good	Pink, translucent	Firm	Normal	..	..	+	..	..	2.5	0.65	74	0.246	0.033	0.098	0.378	
A-63a...F.	12.7	Spaniel. Middle	Good	Pink, translucent	Firm	Normal	..	+	..	..	..	*14.25	3.41	76	4.249	0.334	0.298	1.246	*Left lobe removed April 17, 1907. No iodin.
A-63b...F.	12.7	Spaniel. Middle	Good	Yellow, translucent	Firm	Normal	..	+	..	..	..	*14.0	4.03	71	1.302	0.102	0.092	0.323	*Killed May 22, 1907.
A-64a...M.	2.7	Collie. Pup	Excellent	Purple opaque	Moderate	Reduced	..	..	+	..	..	*2.25	0.36	88	0.108	0.005	0.051	0.300	*Left lobe removed April 17, 1907. No iodin.
A-64b...M.	4.1	Collie. Pup	Excellent	Pink, translucent	Firm	Normal	..	+	..	..	..	*2.3	0.41	82	0.954	0.332	0.415	2.326	*Killed June 5, 1907.
A-65....M.	15.0	Collie. Middle	Excellent	Pink, translucent	Firm	Normal	..	..	+	..	..	3.78	0.98	74	0.892	0.059	0.235	0.910	
A-66....M.	6.81	Cur. Middle	Fair	Pink, opaque	Soft	Reduced	..	..	..	+	+	9.0	2.05	77	0.346	0.059	0.038	0.169	
A-67....M.	34.5	Hound. Middle	Excellent	Red, opaque	Soft	None	..	..	..	..	+	18.7	4.34	76	0.798	0.023	0.042	0.184	
A-68....M.	5.0	Terrier. Young	Fair	Pink, opaque	Soft	Reduced	..	..	..	+	+	3.25	0.66	79	0.138	0.028	0.042	0.209	
A-69....F.	7.0	Cur. Old	Fair	Pink, opaque	Soft	None	..	..	..	+	+	2.75	0.53	80	0.031	0.004	0.011	0.058	
A-70....M.	15.9	Spaniel. Middle	Fair	Pink, opaque	Soft	Reduced	..	..	..	+	..	10.4	2.45	76	0.977	0.061	0.094	0.399	
A-71....M.	5.0	Terrier. Middle	Fair	Pink, opaque	Moderate	Reduced	..	..	..	+	..	3.6	0.786	78	0.323	0.064	0.089	0.410	
A-72....F.	7.7	Cur. Old	Fair	Gray, opaque	Soft	Reduced	..	+	..	..	+	95.0	10.29	88	2.213	0.287	0.023	0.215	Hemorrhagic-cystic complications.
A-73a...M.	8.6	Bull. Young	Good	Red, opaque	Moderate	Reduced	..	..	..	+	..	*2.6	0.44	83	0.185	0.021	0.071	0.420	*Left lobe removed April 25, 1907. Chorea. Five gtt. sat. alc. sol. Iodin.
A-73b...M.	7.1	Bull. Young	Emaciated	Red, translucent	Firm	Reduced	..	+	+	..	..	*2.1	......	..	***	......	......	......	*Died May 4, 1907. Acute distemper. ***Specimen destroyed.
A-74a...F.	5.44	Dachshund. Young	Good	Pink, opaque	Moderate	Reduced	..	..	..	+	..	*3.6	0.50	86	0.261	0.048	0.072	0.521	*Left lobe removed April 25, 1907. No iodin.
A-74b...F.	6.35	Dachshund. Young	Good	Pink, opaque	Moderate	Reduced	..	..	+	..	..	*2.8	0.55	80	0.799	0.125	0.275	1.452	*Killed June 1, 1907.
A-75....M.	6.8	Cur. Middle	Good	Clear, translucent	Firm	Abundant	..	+	..	..	..	6.4	1.69	73	2.702	0.397	0.422	1.599	Spontaneous reversion.
A-76....M.	5.4	Cur. Middle	Fair	Pink, opaque	Soft	None	..	..	..	+	+	6.4	1.44	77	0.222	0.041	0.034	0.154	
A-77....M.	31.0	Collie. Old	Fair	Gray, opaque	Moderate	None	..	..	..	..	+	300.0	52.38	83	2.410	0.070	0.016	0.092	Iodin calculated from left lobe. Old hemorrhages. Neoplasm.
A-78....M.	9.9	Bull. Middle	Good	Pink, translucent	Moderate	Reduced	..	..	..	+	..	2.9	0.77	73	0.399	0.039	0.137	0.519	
A-79....M.	13.6	Beagle. Old	Good	Pink, opaque	Soft	None	..	..	..	..	+	37.0	7.69	79	0.473	0.035	0.012	0.061	
A-80....F.	11.7	Terrier. Middle	Good	Pink, translucent	Firm	Normal	..	+	..	..	..	8.24	1.29	84	1.091	0.093	0.132	0.846	Spontaneous reversion. Pregnant.
A-81....F.	6.2	Terrier. Middle	Excellent	Pink, translucent	Moderate	Normal	..	+?	+	..	..	7.99	1.71	78	1.842	0.297	0.230	1.077	
A-82....M.	15.0	Collie. Middle	Good	Pink, translucent	Firm	Normal	+	..	+?	..	..	1.43	0.25	83	0.200	0.013	0.139	0.800	
A-83....M.	11.8	Cur. Middle	Fair	Pink, translucent	Firm	Normal	+?	..	+	..	..	3.4	0.65	80	0.383	0.032	0.112	0.580	Iodin calculated from left lobe.
A-84....F.	12.7	Terrier. Old	Fair	Pink, translucent	[illegible]	Reduced	[illegible]	[illegible]	+	[illegible]	[illegible]	3.0	0.54	82	0.400	0.031	0.132	[illegible]	

																			as for 2 lobes.
A-21...M.	9.0	Hound. Middle	Fair	Pink, fleshy	Moderate	Reduced	..	..	..	+	..	2.3	0.6	74	0.061	0.006	0.026	0.101	
A-22...F.	?	?	?	Yellow-pink	Firm	Reduced	..	..	+	+	..	5.1	1.63	68	0.425	?	0.082	0.261	
A-23...F.	4.5	Terrier. Old	Fair	Pink	Moderate	None	..	..	..	..	+	5.0	0.96	81	0.615	0.135	0.123	0.640	
A-24...M.	15.9	Spaniel. Middle	Fair	Pink, fleshy	Soft	None	..	..	..	..	+	7.2	1.4	80	0.084	0.005	0.012	0.061	
A-25...M.	11.3	Hound. Middle	Fair	Yellow, pink	Firm	Normal	..	+	..	..	..	8.6	2.27	74	4.676	0.351	0.543	2.060	A reverted glandular hyperplasia (spontaneous).
A-26a...F.	2.4	Terrier. Pup	Fair	Yellow, pink	Firm	Reduced	+	..	..	..	..	*0.24	0.04	83	0.092	0.038	0.380	2.30	*Right lobe removed Feb. 15, 1907. Fed 15 gtt. sat. als. sol. iodin.
A-26b...F.	4.0	Terrier. Pup	Excellent	Clear, yellow, translucent.	Firm	Normal	+	..	..	..	..	*0.305	0.06	80	0.215	0.053	0.705	3.467	*Killed April 2, 1907. Had grown rapidly. Muscle—slightest trace iodin.
A-27a...F.	1.85	Terrier. Pup	Fair	Yellow-pink	Firm	Reduced	+	..	..	..	..	*0.25	0.07	72	0.062	0.033	0.248	0.886	*Right lobe removed Feb. 15, 1907. No iodin administered.
A-27b...F.	1.53	Terrier. Pup	Emaciated	Yellow-pink	Firm	Reduced	..	..	+	..	..	*0.15	0.025	83	0.038	0.024	0.253	1.52	*Died April 2, 1907. Pneumonia. Iodin—slightest possible trace in muscle.
A-28...M.	11.3	Terrier. Middle	Good	Pink, fleshy	Soft	None	..	..	..	..	+	8.4	1.54	82	0.035	0.003	0.004	0.023	
A-29...M.	5.4	Collie. Pup	Good	Red, fleshy	Soft	None	..	..	..	..	+	4.8	0.44	88	0.031	0.006	0.006	0.069	
A-30...F.	14.5	Bull. Middle	Fair	Yellow-pink	Moderate	Reduced	..	+	..	+	..	8.25	1.98	76	2.423	0.167	0.293	1.224	Beginning reversion.
A-31...F.	9.07	Collie. Pup	Good	Yellow, translucent	Firm	Normal	+	..	+	..	..	2.2	0.487	77	0.631	0.069	0.286	1.296	
A-32...M.	5.9	Beagle. Young	Poor	Gray-pink	Moderate	Reduced	..	+	..	+	+	29.8	7.24	75	0.449	0.076	0.015	0.062	Probably marked glandular.
A-33...M.	8.16	Terrier. Young	Good	Pink, fleshy	Moderate	Reduced	..	+	..	+	..	25.0	5.75	77	1.771	0.216	0.071	0.308	Reverting, spontaneously.
A-34...M.	5.6	Terrier. Middle	Fair	Red-yellow	Moderate	Reduced	..	..	..	+	..	4.9	0.72	85	0.615	0.173	0.125	0.854	
A-35...M.	11.8	Spaniel. Middle	Good	Red-opaque	Soft	Reduced	..	..	..	+	..	22.0	5.75	74	1.679	0.142	0.076	0.292	
A-36...M.	10.0	Terrier. Middle	Good	Yellow-pink	Moderate	Reduced	..	+	..	+	..	7.0	2.08	70	1.823	0.183	0.262	0.784	Reverting, spontaneously.
A-37...M.	11.0	Hound. Middle	Poor	Pink-opaque	Moderate	Reduced	..	..	..	+	+	40.0	11.06	72	4.015	0.365	0.100	0.363	
A-38...M.	6.3	Bull terrier. Pup	Excellent	Clear, yellow, translucent	Firm	Normal	+	..	..	..	..	1.3	0.31	77	0.984	0.156	0.757	3.205	
A-39...F.	6.3	Terrier. Middle	Fair	Gray, translucent	Firm	Normal	..	..	+	..	..	1.7	0.44	74	0.108	0.017	0.063	0.243	
A-40...M.	14.0	Setter. Middle	Good	Yellow-pink	Firm	Reduced	..	..	+	..	..	4.5	1.184	74	0.890	0.062	0.197	0.752	
A-41...F.	5.0	Terrier. Pup	Poor	Fleshy-pink	Soft	None	..	..	..	..	+	5.8	0.87	85	0.046	0.009	0.008	0.053	
A-42...M.	12.7	Pointer. Middle	Good	Yellow-pink	Firm	Normal	+	..	+	..	..	6.5	1.56	76	1.271	0.100	0.195	0.815	
A-43...F.	6.0	Terrier. Middle	Good	Clear, yellow, translucent	Firm	Normal	..	+	..	..	..	1.25	0.115	91	0.415	0.039	0.332	3.608	
A-44a...F.	7.7	Six months	Poor	Red, gray	Moderate	Reduced	..	..	..	+	+	*40.0	8.3	79	1.021	0.132	0.025	0.123	*Right lobe removed March 14, 1907. Gland hemorrhagic.
A-44b...F.	7.7	x months	Poor	Red, gray	Moderate	Reduced	..	..	..	+	+	*25.0	3.74	85	0.288	0.037	0.011	0.	und infection after 2 days. Half left lobe used for iodin, te amount.
A-45a...M.	6.3	iddle	Good	Pink, opaque	Soft	None	..	..	..	..	+	*4.0	0.75	81	0.015	0.002	0.004	0.	e removed, March 14, 1907.
A-45b...M.	6.3	iddle	Good	Pink, opaque	Soft	None	..	..	..	..	+	*1.1	0.24	78	0.015	0.002	0.013	0.	nfected, March 16, 1907. Half + l. lobe used for iodin—te amount.
A-46...M.	10.4	le	Good	Gray, translucent	Firm	None	..	..	..	..	+	3.35	0.685	80	0.092	0.008	0.027	0.	
A-47...F.	6.3	oung	Good	Pink, opaque	Moderate	None	..	..	..	..	+	8.0	1.58	80	0.013	0.002	0.002	0.	
A-48...M.	13.6	iddle	Good	Clear, yellow, translucent	Firm	Normal	..	+	..	..	..	3.1	0.86	72	1.753	0.128	0.565	2.	d colloid, using strict classification.
A-49...F.	5.4	le	Fair	Pink, translucent	Firm	Normal	+	..	+	..	..	1.7	0.54	68	0.261	0.048	0.153	0.	
A-50...F.	17.0	le	Good	Pink, translucent	Firm	Reduced	..	+	+	..	..	16.1	4.69	70	2.021	0.119	0.125	0.	ous reversion.
A-51a...M.	3.2	iddle	Fair	Pink, translucent	Moderate	Reduced	..	+	..	..	..	*22.1	4.47	79	3.160	0.987	0.138	0.	removed March 29, 1907. Fed desiccated thyroids (com-l).
A-51b...M.	3.0	iddle	Emaciated	Pink, translucent	Moderate	Normal	..	+	..	..	..	*23.1	5.85	74	5.669	1.889	0.245	0.	il 4, 1907. Pneumonia. Received 6 tablets, each 5 grains.
A-52a...F.	2.7	up	Fair	Pink, opaque	Soft	None	..	..	..	+	+	*3.6	0.52	85	0.215	0.079	0.057	0.	e removed March 29, 1907. Fed iodin, 10 gtt. sat. alc. sol.
A-52b...F.	2.8	up	Good	Clear, yellow	Firm	Normal	..	+	..	..	..	*2.0	0.51	74	1.630	0.563	0.815	3.	pril 23, 1907.
A-53...F.	9.0	iddle	Good	Gray-pink	Moderate	Reduced	..	+	..	+	..	6.9	1.55	77	0.547	0.060	0.079	0.	
A-54...M.	5.4	iddle	Good	Red, opaque	Soft	None	..	..	..	..	+	21.1	3.38	84	0.155	0.028	0.028	0.	
A-55a...M.	7.27		Poor	Purple, opaque	Soft	None	..	..	..	+	+	*72.0	13.15	82	0.610	0.083	0.008	0.	removed April 1, 1907. Cretinoid dog.
A-55b...M.	6.36		Poor	Pink, opaque	Soft	None	..	..	..	+	..	*57.2	11.97	78	16.746	2.633	0.292	1.	pril 8, 1907. Fed iodin, 7 gtt. sat. alc. sol.
A-56...F.	7.3	iddle	Good	Clear, yellow	Firm	Normal	+	..	+	..	..	1.5	0.38	74	0.477	0.065	0.318	1.	
A-57...F.	6.8	ddle	Fair	Pink-yellow	Firm	Normal	..	..	+	..	..	3.1	0.87	72	0.569	0.084	0.183	0.	
A-58...F.	5.0	oung	Poor	Pink, opaque	Moderate	Reduced	..	+	..	+	..	5.82	1.34	76	0.762	0.152	0.131	0.	
A-59...F.	11.0		Good	Pink translucent	Moderate	Reduced	..	+	..	+	..	4.29	1.007	76	0.634	0.058	0.148	0.	
A-60...F.	5.3	oung	Good	Pink, opaque	Soft	Reduced	..	..	..	+	..	16.97	3.6	79	0.608	0.115	0.035	0.	
A-61...F.	4.9	oung	Good	Pink, opaque	Soft	Reduced	..	..	..	+	+	5.09	0.8	84	0.185	0.037	0.036	0.	
A-62...M.	7.3	Middle	Good	Pink, translucent	Firm	Normal	..	..	+	..	..	2.5	0.65	74	0.246	0.033	0.098	0.378	
A-63a...F.	12.7	Spaniel. Middle	Good	Pink, translucent	Firm	Normal	..	+	..	..	..	*14.25	3.41	76	4.249	0.334	0.298	1.246	*Left lobe removed April 17, 1907. No iodin.
A-63b...F.	12.7	Spaniel. Middle	Good	Yellow, translucent	Firm	Normal	..	+	..	..	..	*14.0	4.03	71	1.302	0.102	0.092	0.323	*Killed May 22, 1907.
A-64a...M.	2.7	Collie. Pup	Excellent	Purple opaque	Moderate	Reduced	..	..	+	..	..	*2.25	0.36	88	0.108	0.005	0.051	0.300	*Left lobe removed April 17, 1907. No iodin.
A-64b...M.	4.1	Collie. Pup	Excellent	Pink, translucent	Firm	Normal	..	+	..	..	..	*2.3	0.41	82	0.954	0.332	0.415	2.326	*Killed June 5, 1907.
A-65...M.	15.0	Collie. Middle	Excellent	Pink, translucent	Firm	Normal	..	..	+	..	..	3.78	0.98	74	0.892	0.059	0.235	0.910	
A-66...M.	6.81	Cur. Middle	Fair	Pink, opaque	Soft	Reduced	..	..	..	+	+	9.0	2.05	77	0.346	0.059	0.038	0.169	
A-67...M.	34.5	Hound. Middle	Excellent	Red, opaque	Soft	None	..	..	..	..	+	18.7	4.34	76	0.798	0.023	0.042	0.184	
A-68...M.	5.0	Terrier. Young	Fair	Pink, opaque	Soft	Reduced	..		..	+	+	3.25	0.66	79	0.138	0.028	0.042	0.209	
A-69...F.	7.0	Cur. Old	Fair	Pink, opaque	Soft	None	..	..	..	+	+	2.75	0.53	80	0.031	0.004	0.011	0.058	
A-70...M.	15.9	Spaniel. Middle	Fair	Pink, opaque	Soft	Reduced	..	..	..	+	..	10.4	2.45	76	0.977	0.061	0.094	0.399	
A-71...M.	5.0	Terrier. Middle	Fair	Pink, opaque	Moderate	Reduced	..	..	..	+	..	3.6	0.786	78	0.323	0.064	0.089	0.410	
A-72...F.	7.7	Cur. Old	Fair	Gray, opaque	Soft	Reduced	..	+	..	..	+	95.0	10.29	88	2.213	0.287	0.023	0.215	Hemorrhagic-cystic complications.
A-73a...M.	8.6	Bull. Young	Good	Red, opaque	Moderate	Reduced	..	..	..	+	..	*2.6	0.44	83	0.185	0.021	0.071	0.420	*Left lobe removed April 25, 1907. Chorea. Five gtt. sat. alc. sol. Iodin.
A-73b...M.	7.1	Bull. Young	Emaciated	Red, translucent	Firm	Reduced	..	+	+	..	..	*2.1	......	..	***	......	......	......	*Died May 4, 1907. Acute distemper. ***Specimen destroyed.
A-74a...F.	5.44	Dachshund. Young	Good	Pink, opaque	Moderate	Reduced	..	..	+	..	..	*3.6	0.50	86	0.261	0.048	0.072	0.521	*Left lobe removed April 25, 1907. No iodin.
A-74b...F.	6.35	Dachshund. Young	Good	Pink, opaque	Moderate	Reduced	..	..	+	..	..	*2.8	0.55	80	0.799	0.125	0.275	1.452	*Killed June 1, 1907.
A-75...M.	6.8	Cur. Middle	Good	Clear, translucent	Firm	Abundant	..	+	..	..	..	6.4	1.69	73	2.702	0.397	0.422	1.599	Spontaneous reversion.
A-76...M.	5.4	Cur. Middle	Fair	Pink, opaque	Soft	None	.	..	..	+	+	6.4	1.44	77	0.222	0.041	0.034	0.154	
A-77...M.	34.0	Collie. Old	Fair	Gray, opaque	Moderate	None	..	..	..	..	+	300.0	52.38	83	2.410	0.070	0.016	0.092	Iodin calculated from left lobe. Old hemorrhages. Neoplasm.
A-78...M.	9.9	Bull. Middle	Good	Pink, translucent	Moderate	Reduced	..	..	..	+	..	2.9	0.77	73	0.399	0.039	0.137	0.519	
A-79...M.	13.6	Beagle. Old	Good	Pink, opaque	Soft	None	..	..	..	..	+	37.0	7.69	79	0.473	0.035	0.012	0.061	
A-80...F.	11.7	Terrier. Middle	Good	Pink, translucent	Firm	Normal	..	+	..	..	..	8.24	1.29	84	1.091	0.093	0.132	0.846	Spontaneous reversion. Pregnant.
A-81...F.	6.2	Terrier. Middle	Excellent	Pink, translucent	Moderate	Normal	..	+	+	..	..	7.99	1.71	78	1.842	0.297	0.230	1.077	
A-82...M.	15.0	Collie. Middle	Good	Pink, translucent	Firm	Normal	+	..	+	..	..	1.43	0.25	83	0.200	0.013	0.139	0.800	
A-83...M.	11.8	Cur. Middle	Fair	Pink, translucent	Firm	Normal	+	..	+	..	..	3.4	0.65	80	0.383	0.032	0.112	0.580	Iodin calculated from left lobe.
A-84...F.	12.7	Terrier. Old	Fair	Pink, translucent	Moderate	Reduced	..	..	+	..	..	3.0	0.54	82	0.400	0.031	0.133	0.741	
A-85...F.	3.3	Terrier. Middle	Fair	Pink, opaque	Moderate	None	..	..	..	+	+	2.0	0.31	84	0.138	0.042	0.069	0.445	
A-86...M.	9.0	Cur. Middle	Excellent	Clear, yellow, translucent	Firm	Normal	..	+	..	..	..	3.2	1.02	68	3.325	0.358	1.039	3.261	
A-87...F.	4.7	Cur. Young	Fair	Clear, yellow, translucent	Firm	Normal	+	..	..	..	..	1.3	0.29	78	1.384	0.294	1.064	4.772	
A-88...F.	5.0	Terrier. Young	Good	Clear, yellow, translucent	Firm	Normal	..	..	+	..	..	1.5	0.25	83	0.107	0.021	0.071	0.428	
A-89...M.	10.4	Terrier. Old	Good	Clear, yellow, translucent	Firm	Normal	..	+	+	..	..	2.2	0.42	84	0.664	0.063	0.302	1.443	
A-90...M.	5.4	Terrier. Old	Fair	Clear, pink, translucent.	Firm	Abundant	..	+	..	..	..	17.1	4.27	76	6.659	1.233	0.389	2.563	
A-91...M.	10.0	Terrier. ?	Fair	Pink, translucent	Moderate	Abundant	..	+	..	+	..	67.7	16.4	75	9.124	0.912	0.134	0.538	
A-92...F.	8.2	Terrier. Middle	Fair	Pink, translucent	Moderate	Normal	..	..	+	..	..	3.5	0.65	81	0.666	0.081	0.190	1.028	Pregnant.
A-93...F.	7.0	Terrier. Middle	Excellent	Clear, yellow, translucent	Firm	Normal	+	+	..	..	..	3.2	0.62	80	1.538	0.218	0.480	2.480	
A-94a...F.	2.15	Terrier. Middle	Fair	Pink, translucent	Firm	Normal	..	..	+	..	..	*1.5	0.28	81	0.184	0.085	0.122	0.657	*Left lobe removed May 11, 1907. No iodin.
A-94b...F.	1.95	Terrier. Middle	Poor	Pink, translucent	Firm	Normal	..	..	+	..	..	*1.0	0.21	79	0.215	0.110	0.215	1.024	*Died May 25, 1907. Mercuric chlorid poisoning.
A-95a...F.	5.9	Cur. Middle	Fair	Red, translucent	Firm	Normal	..	+	..	..	..	*5.1	1.2	76	1.284	0.218	0.251	1.076	*Left lobe removed May 25, 1907. Isthmus. No iodin.
A-95b...F.	5.67	Cur. Middle	Fair	Pink, translucent	Firm	Normal	..	+	..	..	..	*3.4	0.77	74	0.554	0.097	0.163	0.719	*Killed June 6, 1907.
A-96...F.	4.5	Terrier. Young	Good	Red, opaque	Moderate	None	..	..	..	+	+	1.7	0.28	83	0.185	0.041	0.109	0.660	
A-97...M.	6.0	Prince Charles. Young	Good	White-yellow	Hard	None	..	+	..	..	..	1.89	0.48	74	0.154	0.025	0.081	0.320	Extensive calcification of capsule lobes very small.
A-98...F.	5.9	Cur. Middle	Fair	Pink, translucent	Firm	Normal	+	..	..	..	..	3.65	0.95	74	1.891	0.320	0.512	1.990	
A-99...F.	5.4	Terrier. Young	Good	Pink, opaque	Soft	None	..	..	..		+	7.7	1.32	83	0.102	0.019	0.013	0.077	
A-100...F.	5.9	Cur. Middle	Good	Pink, translucent	Moderate	Reduced	..	+	+	..	..	4.6	1.18	74	0.979	0.166	0.213	0.830	Reverting.
A-101...M.	5.4	Cur. ?	Fair	Pink, fleshy	Soft	Reduced	..	..	..	+	+	24.0	5.15	78	1.344	0.249	0.056	0.261	
A-102...F.	3.6	Terrier. Middle	Good	Pink, fleshy	Soft	None	..	..	..	..	+	5.0	0.64	87	0.077	0.021	0.015	0.120	
A-103...M.	8.6	Spaniel. Middle	Good	Pink, translucent	Moderate	Normal	..	..	+	..	..	1.3	0.22	83	0.107	0.012	0.083	0.480	
A-106a...F.	11.8	Bull. Middle	Fair	Brown, translucent	Firm	Normal	..	+	..	..	..	*29.5	3.19	89	0.986	0.083	0.033	0.308	*Right lobe removed June 25, 1907. No iodin.
A-106b...F.	9.52	Bull. Middle	Fair	Brown, translucent	Firm	Normal	..	+	+	..	..	*15.0	2.67	82	0.987	0.066	0.066	0.369	*Approximately half of left lobe removed July 15, 1907. No iodin.
A-106c...F.	9.40	Bull. Middle	Poor	Pink, translucent	Moderate	Reduced	..	..	+	+	..	*3.0	0.49	84	0.296	0.031	0.099	0.554	*Approximately half of remaining portion of left lobe removed, Sept. 10, 1907. No iodin.
A-106d...F.	9.10	Bull. Middle	Poor	Pink, opaque	Moderate	None	..	..	..	..	+	*4.5	0.60	..	0.293	0.039	0.022	0.115	*Remaining portion of left lobe removed Dec. 7, 1907. No iodin.
A-106e...F.	11.4	Bull. Middle	Good	Gray red	Firm	Reduced	..	..	..	+	+	*0.95	0.23	75	0.099	0.009	0.095	0.410	*Killed Jan. 21, 1908. No trace of thyroid lobes; 2 accessory aortic thyroids. Weight 0.95 gms.; 5 gtt. syrup ferrous iodid and 6 5-gr. tablets desiccated thyroid.
A-106f...F.	11.4	Bull. Middle	Good	Atrophic thymus		....	..	..	..	..	..	*7.6	2.49	67	0.046	0.004	0.006	0.018	*Killed Jan. 21, 1908. Spec. thymus with no visible access. thyroids.
A-104...F.	7.71	Terrier. Middle	Good	Yellow, translucent	Firm	Normal	..	+	..	..	..	*3.5	0.70	80	1.786	0.232	0.510	2.738	*Admitted May 17, 1907. Right and half of left lobes removed Sept. 10, 1907. Between pregnancies.
A-107a...F.	4.54	Cur. Young	Fair	Yellow, translucent	Firm	Normal	..	+	..	..	..	4.1	0.82	41	0.709	0.131	0.173	0.865	Right and half left lobes removed July 15, 1907; 12 gms. desiccated thyroid fed before operation "Spec. C." Hyperplastic.
A-108a...F.	4.54	Cur. Young	Fair	Yellow, translucent	Firm	Normal	..	+	..	..	..	*2.1	0.34	84	0.923	0.203	0.439	2.714	*Right and half left lobes removed July 15, 1907: 11 gms. desiccated thyroid fed before operation "Spec. D." Normal.
A-109a...F.	5.4	Hound. Eight months	Fair	Pink, fleshy	Soft	None	..	..	..	..	+	*33.5	4.44	92	0.301	0.056	0.009	0.070	Right lobe removed Oct. 30, 1907.
A-110a...M.	8.5	Setter. Six months	Poor	Pink, fleshy	Soft	None	..	..	..	..	+	41.0	5.33	87	0.330	0.038	0.008	0.031	
A-111...M.	12.7	Bull terrier. Middle	Good	Yellow, translucent	Firm	Normal	..	+	..	..	..	*47.0	12.35	73	32.480	2.557	0.691	2.630	*Fed 130 gtt. syrup ferrous iodid. Killed Jan. 15, 1908. Reversion of marked glandular.
A-112...F.	5.4	Cur. Young	Good	Pink, translucent	Moderate	Reduced	..	..	+	+		*4.15	0.74	82	0.246	0.072	0.078	0.332	*Left and two-thirds right lobes removed Jan. 15, 1908. Early preg.
A-113...F.	5.39	Terrier. Young	Good	Yellow, translucent	Firm	Normal	..	+	+	..		*4.7	0.99	79	0.507	0.086	0.108	0.513	*Left and two-thirds right lobes removed Jan. 15, 1908. Late pregnancy. Died tetany Jan. 24, 1908; aborted.

* Weights are, in most cases, abridged to a single figure to right of decimal point. This should be noted in referring to the figures in the iodin column, for the latter were computed on the actual weights.

istration of continued minute doses of iodin even in the exophthalmic hyperplasias.

Sheep.—An hyperplasia which had undergone spontaneous reversion contained 0.455 mg. iodin per gm. of fresh thyroid, while four marked hyperplasias showed in two cases no estimatable amount, and in the other two iodin contents of 0.014 and 0.019 mg. per gm. of fresh thyroid respectively. These observations suggest that here, too, the iodin was proportional to the colloid, and inversely proportional to the degree of glandular hyperplasia.

Horses.—Two thyroids in the anatomic stage of moderate glandular hyperplasia showed 0.054 and 0.091 mg. iodin per gm. of fresh thyroid respectively.

Calves.—A large parenchymatous goiter in the stage of marked glandular hyperplasia contained 0.042 mg. iodin per gm. of fresh thyroid.

Cat and Bear.—On examination a histologically normal cat's thyroid showed 0.154 mg. of iodin per gm. of fresh gland, while the thyroid from a young bear in the stage of early hyperplasia contained 0.081 mg. iodin per mg. of fresh gland.

These observations, though still scanty, suggest that other animals in general obey laws similar to those found for the dog, and also, as pointed out by Baumann, that different animal species have normally different iodin contents—the carnivora having considerably less than the herbivora.

In reviewing the investigations of Baumann, Roos, Oswald and Weiss we find that direct comparisons with our work are impossible, because the methods of iodin determinations differed in some details, but especially because no histologic classification was used, which renders it impossible to estimate what relation iodin bore to the gland structure. However, a summary of their results may be of interest. Baumann and Roos,[35] working with sheep's thyroids, found that their iodin content varied with the regions from which the glands were taken, being least in the goitrous regions, e. g., Frieburg glands contained 1.06 mg. per gm. of dried gland; Elberfelt glands contained 3.40 mg. per gm. of dried gland; Paris glands contained 1.70 mg. per gm. of dried gland.

Baumann,[36] working with human glands, found the same regional differences in the iodin content of normal adult glands as was noted for sheep, e. g., Hamburg glands contained 0.83 mg. iodin per gm. of dried gland; Berlin glands contained 0.90 mg. iodin per gm. of dried gland; Freiburg glands contained 0.33 mg. iodin per gm. of dried gland.

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[35] Ztschr. f. physiol. Chem., 1895-6, xxi, 480.

[36] Ztschr. f. physiol. Chem., 1896-7, xxii, 1.

He also found that the same differences held for infants and children. In goiters obtained in Freiburg he found 0.09 mg. per gm. of dried gland to be the average iodin content. From these observations he concluded that thyroids from animals in goitrous districts have normally less iodin than glands from non-goitrous regions, and that in uncomplicated goiters it was exceedingly low.

Oswald,[37] working with normal (?) glands from the several provinces of Switzerland, found that the glands contained as much iodin (0.916 mg. per gm. of dried gland) as normal glands from non-goitrous districts, but that goiters (glands weighing 95 gms. or more) contained, on the average, about half as much iodin per gm. of dried thyroid. Weiss[38] found the average iodin content in human glands to be 0.56 mg. per gm. of dried glands for Silesia.

OBSERVATIONS ON THE IODIN CONTENT OF OTHER TISSUES.

From the examination of the livers and muscles in three cases, in two of which iodin had been administered, the thyroids showing a high iodin content, only the slightest possible trace of iodin was present in two pieces of muscle, and none in the livers. We think these findings suggest that the amount of iodin normally present in tissues other than the thyroid is a negligible quantity.

Recently Loeb,[39] from a rather extensive study of the tissues (rabbit) after the administration of known quantities of potassium iodid, arrived at similar conclusions., viz., that after ninety-six hours following the administration of KI to rabbits, mere traces only could be detected in the lungs, kidneys, skin and blood.

If Justus'[40] contention that iodin is present in all cell nuclei be true, it must be so small in amount that it is not determinable by the methods adopted by us. In one case in which two accessory thyroids were examined, an animal to which small amounts of iodin had been administered, a rather high iodin content (0.1 mg.) was found. This is to be expected, since the accessory thyroids (examined histologically in a large number of cases) show similar anatomic changes to those occurring in the main lobes.

The thymus from the same case also showed a relatively large amount

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37. Ztschr. f. physiol. Chem., 1897, xxiii, 265.
38. Münch. med. Wchnschr., 1897, xliv, 6.
39. Arch. f. exp. Path. u. Pharmakol., lvi, 320.
40. Virchow's Archiv., Bd. clxx, S. 501.

(0.046 mg.) of iodin. Gross inspection of the gland as well as study of the portions taken for microscopic examination, failed to reveal accessory thyroids. This is at variance with Cunningham and Mendel,[41] who claim that when iodin is present in the thymus it is probably due to the presence of accessory thyroids. In fairness, however, it may be stated here that there is another possible explanation of the presence of iodin in the dog's thymus, viz., that over 20 per cent. of the dogs show persistent cystic dilatation of the embryonal thymic ducts (first described by Remak), and that the iodin present may be the result of excretion into these spaces rather than evidence of its existence in the true functional thymic tissue. Baumann[42] was the first to point out that the thymus contained iodin. He also showed that by feeding dogs with fresh thymus, as compared with feeding with fresh muscle,[43] the iodin content could be raised; this could also be done in the case of thyroid glands by feeding with dog biscuit or sea fish. That the thymus is in many ways related to the thyroid in function has been pointed out by many observers from several points of view. For example, Mikulicz[44] and others have noted the mildly beneficial effects of feeding thymus in goiter; it has also been pointed out that in parenchymatous goiter and in cretins the thymus is generally persistent or even enlarged.[45]

Whether iodin is in any way related to the therapeutic value of thymus or its associated persistence in cretinoid states is a subject on which one of us (Marine) is now collecting data.

OBSERVATIONS ON COMMERCIAL DESICCATED THYROID.

As pointed out in a previous paper by one of us, a large proportion of the sheep in certain districts have enlarged (hyperplastic) thyroids, and it occurred to the writer to visit one of the larger commercial laboratories where desiccated thyroid is prepared to see what kind of glands were being used. It was found that they were using hyperplastic as well as normal glands in preparing their medicinal products. In the light of the findings of Baumann, Oswald, Roos and the authors, viz.: (1) that the iodin content, in general, varies with the amount of colloid; (2) that in general the colloid varies inversely with the degree of glandular hyperplasia; (3) that the iodin content varies inversely with the degree of glandular hyperplasia, and (4) that the physiologic activity of thyreoglobulin varies directly with the amount of iodin in organic combination, it becomes necessary to determine the iodin content of the various thyroid preparations. Accordingly, one of the firms prepared for us samples made from what they considered (1) normal glands (gross appearance), and (2) hyperplastic glands (gross appearance). We add the iodin contents of these specimens, and for comparison the iodin contents of a sample obtained in the market, together with a determination made from histologically normal glands.

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[41] Am. Jour. Physiol., 1900, iii, 285.

[42] München. med. Wchnschr., 1896, liii, 311.

[43] Ztschr. f. physiol. Chem., 1896-7, xxii, 14.

[44] Berl. klin. Wchnschr., 1895, xxxii, S. 342.

[45] Marie, Gaz. d. hôp., 1893, p. 202; also Hektoen, Internat. Med. Mag., 1896, iv, 584.

Specimen "C" from hyperplastic glands,, 0.292 mg. iodin per gm. of dried gland; specimen "D" from normal glands, 1.092 mg. iodin per gm. of dried gland; specimen "E" obtained in the market, 1.538 mg. iodin per gm. of dried gland; specimen "F" histologically normal glands, 1.769 mg. iodin per gm. of dried gland.

These four analyses indicate that the preparation made from the hyperplasias contains only one-sixth the amount of iodin present in the histologically normal glands, while a sample obtained in the market contained a third more iodin than the sample made from supposedly normal glands. There being no reason to suppose that iodin was added, no attempt was made to determine whether there was any free iodin. Since the manufacturing firms use both the hyperplastic and the normal glands in the preparation of their therapeutic products, it follows that different samples must contain varying amounts of iodin. Aufrecht examined thyroid tablets made from hog's glands obtained from different localities and found great variations in the iodin content.

Experiments with feeding specimens "C" and "D" desiccated thyroid were undertaken and, although accidentally incomplete, are suggestive enough to be mentioned here. Two dogs (A-107 and A-108) of the same age, breed and weight were fed on equal amounts (11 gms.) of specimens "C" and "D" respectively in eighteen days. The dog fed with specimen "C" (hyperplasia) did not lose weight, and the amount of iodin per gm. of fresh thyroid was 0.173 mg. (gland taken twenty-one days after last dose of substance); while the other dog (A-108) fed on specimen "D" (normal glands) lost 454 gms. in weight in eighteen days of feeding; the amount of iodin per gm. of fresh thyroid was 0.439 mg. (gland taken twenty-one days after last dose). This suggests, as Oswald and Roos have pointed out, that the activity of the thyroid substance varies with the amount of iodin in organic combination; but it is not in contradiction with the possibility and, indeed, the probability, as mentioned by Hunt[46] and one of us,[1] that the substance, in the absence of iodin, may have other activities.

GENERAL DISCUSSION.

The importance of a histologic basis of classification in goiter can not be overestimated. Virchow, as early as 1863, pointed out the great confusion which then existed in the classification of thyroid diseases and also the dangers to which it was leading, viz., the interference with the advance in our knowledge of goiter both anatomically and clinically. In the first place, the classification must be rigid, and second, it must be dependent on the three natural anatomic divisions., viz., (1) normal glands; (2) colloid glands; (3) hyperplasia. In an organ whose structure is so manifestly affected by a variety of systemic conditions it is clearly impossible to make use of any other factor than anatomy as a point of departure. Little need be added relative to the anatomic descriptions of the groupings already given. It is to be regretted that more normal glands were not found, though it seems unlikely that iodin determinations in a larger number of normal glands would have materially changed the relative importance, and it is this feature, rather than the actual figures, that we consider important.

Comparison of the iodin determinations with the corresponding histologic groupings, as shown in Tables 2, 3, 4 and 5, permit the deduction of several important general conclusions which bring the relationship of iodin to the structure of the thyroid closer than has heretofore been suspected. Some of these relationships may be again referred to, for the sake of emphasis: the percentage of iodin in general varies with the amount of stainable colloid, as was first pointed out by Oswald. To this rule there is an apparent contradiction in the normal and colloid gland, but this can be explained by the fact that there are quite wide limits in the percentage of iodin above the amount necessary for the maintenance of normal structure, and this reserve iodin, so to speak, produces no detectable microscopical changes. It also appears to be a general law that the colloid material in general varies inversely with the degree of glandular hyperplasia, and third, it is shown that the iodin content varies inversely with the degree of glandular hyperplasia.

In the analyses of the individual members of the separate groups there are many apparent exceptions also to the last two general laws mentioned, and these exceptions rather suggest that while iodin is the main object and factor governing thyroid activity, there are other conditions as well which influence the gland structure. This, indeed, would be probable if goiter is considered as a manifestation of a nutritional disturbance.

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[46] The Journal A. M. A., 1907, p. 1323.

As pointed out above, there are wide variations between the amount of iodin necessary to maintain normal structure and the largest amount which can be held in organic combination by the colloid (thyreoglobulin), and within these limits the microscopic changes in the structure are too slight to be estimated accurately, though there must be wide differences in structure that are not to be detected by present microscopic methods. In view of this factor of error in normal and colloid glands, more importance should be attached to the early hyperplasias and to the minimal amount of iodin necessary to start hyperplastic changes. This minimal amount is found to be quite constant, as shown in Table 5, being 0.173 mg. iodin per gm. of fresh thyroid for the "normal X early" glands, 0.217 mg. for the "colloid X early," and 0.139 mg. for the pure early glands.

Passing to the hyperplasias, here, too, we find a difficult factor to determine by histologic examination for the reason that microscopically it is often difficult to decide whether a gland is reverting from a more marked hyperplasia or is undergoing secondary hyperplasia; in the former case the iodin content would be higher than in the latter. So that, in view of these known difficulties, it is probable that future workers, while laying most stress on the anatomic structure, will have to take cognizance of the iodin content as well, in order to group the glands accurately and to estimate their functional activity. Nevertheless, it is clear that these apparent exceptions do not materially affect the importance established for iodin in its relation to thyroid structure and gland activity, and, besides, it is probable that all these exceptions could be rationally explained if the complicating factors acquired during the life of the animal were known.

A point worthy of special notice is that the iodin contents of the glands included under double references, as shown in Table 5, fall between the iodin contents of the groups to which they were anatomically referred, though in making up the original tables they were not considered at all, and the results could not in any way be influenced by ideas gained from the original (pure) groups. This additional grouping amounts, in effect, to doubling the evidence in proof of the three laws above mentioned, and also indicates that the hyperplasias, both histologically and chemically, resist arbitrary grouping, but represent a continuous gradation from the normal glands to the marked hyperplasias.

In a previous paper[1] it has been pointed out that the thyroid is not the only tissue affected in the production of glandular hyperplasia (parenchymatous goiter). As has been pointed out by many observers, the lymphoid tissues (spleen, thymus and lymph glands), together with the bone marrow, show quite constant lesions that must be considered integral parts of the general disturbance, and when one recalls the experimental biologic data already mentioned in the introduction it appears highly probable that in the natural occurrence of goiter, as in its artificial production, the underlying process is essentially a "compensatory reaction to some deficiency" rather than that it is a spontaneous thyroid affection. This is a view quite opposite to that held by many students of exophthalmic goiter. That iodin is the most important single factor in this disturbance is further suggested by the fact that the ability of the thyroid to store iodin depends on the degree of glandular hyperplasia rather than on the form or mode of its administration, as shown in Table 9, and also that there is an economy and storage of iodin (somewhat comparable to that of iron), as shown by the fact that there are wide limits in the iodin content between the amount necessary to maintain normal structure and the highest amount of iodin which can be stored in the gland.

In view of the evidence thus far deduced, we believe that goiter must be classed with the nutritional disturbances (diseases) and that as such it will take its place in nosology along with chlorosis, rachitis, status lymphatics, osteomalacia, (?) etc. That there are other factors than iodin influencing the thyroid changes seems to be proved, but there is no experimental evidence that a specific infecting agent as such is one of these factors.

The mode of action of iodin is probably similar to that of iron, calcium and other normal metallic constituents of the body in their relations to normal and disturbed metabolism, viz., that as in the case of iron, calcium, etc., so with iodin, (1) the body practices an economy in its use; (2) there is a normal minimal amount necessary for the body needs, and a variable reserve quantity, and (3) that a deficiency of either element induces anatomical changes in the tissues directly concerned with their storage and elaboration.

Finally, the treatment of simple hyperplasias has close analogies with the treatment of chlorosis, particularly in that the form of iron or iodin administered is not all important, since the ability to take up these metals depends rather on the degree of tissue reaction. And this fact suggests a point in the treatment of symptomatic thyroid hyperplasias that may have considerable practical importance, viz., that the physiologic dose of iodin should be inverse to the degree of glandular hyperplasia.

The reversion to a colloid type, which occurs coincidently with the administration of iodin in a hyperplasia, is the histologic evidence of a cure and not of a degenerative process in the usual interpretation of that term. Colloid glands (goiters) are the nearest normal condition to which the hyperplasias can return, and not only is this true of their gross and histologic appearance, but also of their chemical (iodin) and clinical bearing as well.

The problem of commercial desiccated thyroid is an important one for the pharmacologist and clinician alike, as has already been shown both on the bases of anatomic structure of the thyroids used and on its physiologic activity. Some standard, either chemical or physiologic, is needed, even if in the absence of organically combined iodin the substance is inert. This, however, can not be granted at present, as there is some clinical evidence that these hyperplastic glands during life have a greatly altered secretion which exerts a toxic action on the organism. Whether this activity may be destroyed in the preparation of desiccated thyroid is a very important problem for clinical experiment, particularly when desiccated thyroid is so extensively used in the treatment of thyroid changes histologically similar to those existing in the glands from which the preparations are made.

PROBLEMS OF HUMAN GOITER.

In view of the relations that have been shown to exist between the amount of iodin and the histologic structure of the thyroid in the dog, and in view of the facts thus far collected as to the incidence, distribution, nature and treatment of goitrous conditions in all animals, it seems necessary that similar work be carried out in man, both in goitrous and non-goitrous districts. The essential problems for solution must be the same in man as in animals, and are modified only by man's position in the biologic scale and by the vast complex of acquired conditions—accidental or intentional (social complex, food, migration, locality, medication, etc.).

With fairly definite anatomic criteria established in animals, it seems possible to group and study the human forms. This work is now in progress. As is to be expected, great irregularities are met with on account of complicating factors which are almost always present and make interpretation of the observations difficult. However, the general conditions so far are found to obey the same general laws that were found in the dog. The problem of human goiter at the present time is practically one of a study of toxic (exophthalmic) goiter, since the simpler forms are easily controlled.

The investigations in the past have been largely concerned with the elaborations of methods of treatment or a discussion of the various symptoms and signs. The underlying factors of most of these signs and symptoms are either unknown to us or are common to other nervous and mental affections as well. Further advance in our knowledge as to the nature of the process from the purely clinical side is, therefore, scarcely to be expected. The first step in undertaking a systematic study of exophthalmic goiter, it seems, should be that of providing a definite, strict anatomic classification, checked in every instance by chemical and physiologic examinations of the thyroid, after which we must seek to bring the clinical observations into relation with these findings.[47]

CONCLUSIONS.

1. Iodin is necessary for normal thyroid activity.

2. Iodin is the main index to the physiologic value of the thyroid secretion (thyreoglobulin) to the body.

3. The percentage of iodin varies with the amount of colloid in the several degrees of hyperplasia; the colloid varies inversely with the degree of thyroid hyperplasia; the iodin varies inversely with the degree of thyroid hyperplasia.

4. The colloid gland (goiter) is the quiescent or normal state of a gland which has previously been a glandular hyperplasia and obeys all the biologic laws of a normal gland.

5. In the classification of thyroid changes (excluding infections and neoplasms) four major groups must be recognized, viz.: (1) normal glands, (2) colloid glands, (3) hyperplastic glands (all grades), (4) complications engrafted on any of the three preceding groups.

6. The ability of the thyroid glands to store iodin depends on the degree of glandular hyperplasia rather than on the form or mode of administration of iodin.

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[47] It is impossible to ascertain the anatomical condition of the gland except by histologic examinations, and in the determination of normal glands this is doubly important. It should be pointed out that in a scientific investigation there is no "normal gland for a district," as was stated by Oswald. He considered a gland non-goitrous in Switzerland if it weighed less than 95 gms. (normal adult sea coast glands average 30 to 40 gms). Our standard of normal is borrowed from the sea coast type of gland and in goitrous districts this standard is rarely attained.

7. The optimum therapeutic effects of iodin on the thyroid gland are only obtained with doses vastly smaller than those usually employed.

8. The percentage of iodin which a thyroid may contain is variable, but the minimal percentage necessary for the maintenance of normal gland structure is quite constant.

9. Commercially desiccated thyroid has a very inconstant iodin content and, therefore, has a variable physiologic activity and therapeutic value.

10. The problem of human goiter, both anatomically and chemically, should be investigated along lines similar to those adopted for the dog.

[Note.—We wish to thank Prof. Torald Sollmann for his careful criticisms and suggestions; Prof. W. T. Howard for the privilege of his autopsy material, and Prof. G. W. Crile for the free use of material from his surgical clinic. We are also greatly indebted to Drs. C. H. Lenhart and M. B. Bonta for their skilled assistance in the operations.]

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A DETAILED STUDY OF THE CHANGES OCCURRING IN THE PHYSIOLOGICAL DEGENERATION OF ACTINOSPHÆRIUM EICHORNI.*

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INTRODUCTION.

For a clear understanding of the changes to be described in the series of *Actinosphæria,* the study of which forms the basis of this communication, it is necessary to give a description of a normal *Actinosphærium* and a resumé of Richard Hertwig's work on the physiological degeneration of this animal.

In life, a normal *Actinosphærium* is a spherical cell with numerous radially projecting pseudopodia, regularly distributed over the surface, and each with a homogeneous axis fiber. The protoplasm is sharply divided into a coarsely vacuolated cortical layer, which contains the contractile vacuoles and through which the bases of the axis fibers of the pseudopodia run; and an inner, more finely vacuolated protoplasm, the medulla, in which lie the nuclei and the food vacuoles. The nuclei are situated chiefly in the peripheral layer of the medulla, just beneath the cortex; but a few nuclei are scattered in the deeper parts of the medulla. The number of nuclei varies with the size of the animal. According to R. Hertwig, the nuclei, under normal conditions, vary from 10 to 14 μ in diameter, and are surrounded by a distinct nuclear membrane, and contain nuclear sap and an achromatic linin framework, on which lie the nucleolar substance and the chromatin. He regards the nucleolar substance as identical with the material of which the nucleoli of the tissue cells of metazoa consists. According to Hertwig, in the simplest, but least common conditions, as

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in functional rest and just before division, the nucleolar substance is mixed with the chromatin into a spherical nucleolus or amphinucleolus. Usually, the material of the amphinucleolus is divided, either into two or more small nucleoli, or into dendritically branching processes, which radiate from the center to the periphery and lie on the nuclear framework. The latter arrangement is an indication of energetic nuclear function. He describes nuclei with divided amphinucleolus, in which there is a separation of nucleolar substance and chromatin. In these, the chromatin seeks the peripheral ends of the processes, so that the center of the figure, which he calls the chromatin rosette, appears light.

In his work on the physiological degeneration of *Actinosphærium eichorni,* Richard Hertwig ('04) described a series of important changes affecting the structures of this rhizopod which shed much light upon both the physiology and the pathology of the cell. These may be summarized as follows:

(*a*) *Chromidium.*—In 1902, he first noticed the presence in the plasma of *Actinosphærium* of fine or coarse granules, rods, or even triangular and slightly branched bodies, with the staining reactions of the amphinucleolus and consisting of a mixture of chromatin and nucleolar substance. These masses, the origin of which Hertwig traced to the nucleus, lie both on the plasmatic meshwork and in the vacuoles of the same, and were called chromidia. They occur chiefly in the medulla, but may be present in the cortex. They may be present in starved, as well as in overfed, *Actinosphæria.* Hertwig draws an important distinction between the chromidia above mentioned and the "Chromidialnetz" which he had previously described in the Thalomorphora; the latter he regards as the chief seat of the functional capacity of the cell, and the former he considers superabundant functionless parts of the nucleus which are thrown off to be got rid of, just as the chromidia of egg cells. It is necessary to emphasize here the distinction between chromidia in this sense and the functionally active forms of extranuclear chromatin known variously as "Chromidia," "Chromidialnetz" and "Chromidialapparatus," which, as R. Hertwig, Schaudinn and Goldschmidt have shown, play an important rôle in many protozoan and metazoan cells.

(*b*) *Pigment Formation.*—This occurs in *Actinosphærium* under various conditions in which a considerable amount of nuclear material is destroyed, as just before encysting and in starved cultures. The highest degree of pigmentation occurs in the depression of overfeeding, in connection with marked production of chromidia. The pigment, which Hertwig has traced to the destruction of chromatin, is of a yellowish brown color, and consists of fine refractile particles, which may be isolated or in smaller or larger clumps in the medulla and cortex. The pigment granules often lie about the nuclei. They often beset the peripheral layer of the cortex, from which they are extruded. They may also lie in sequestra, which may be thrown out.

(*c*) *Destruction of Nuclei.*—Of this Hertwig describes three types. (1) Simultaneous solution of all the nuclei to chromidia. (2) The transformation of one or a few nuclei to giant nuclei, which may be thrown out, while the rest of the nuclei are dissolved. (3) The extrusion of the whole medulla with its nuclei.

1. The transformation of all the nuclei to chromidia with the disappearance of the other nuclear constituents was observed first in three animals in an encysting culture; in the place of nuclei they were beset with chromidia. Hertwig explained the phenomenon as due to excessive development on the part of the protoplasm of its normal capacity to destroy nuclei when encysting. Under normal conditions, in encysting *Actinosphæria,* only from ninety to ninety-five per cent. of all the nuclei are dissolved, while in these animals all the nuclei were destroyed.

In his overfeeding experiments also, he produced "chromidial animals" with solution of nuclei. In this instance, he explained the changes on the basis of his well known "Kern-plasma-relation theory."

2. The formation of giant nuclei occurs during the depression associated with overfeeding. The animals are the seat of other changes, such as the loss of pseudopodia and of the distinction between cortex and medulla. The giant nuclei, which are discernible in the living animal, may reach the diameter of 196 μ. The giant nuclei are surrounded by a radiating zone of fine granules. An animal may develop from fifteen to twenty giant nuclei.

Giant nuclear animals die in a few days, but before death one or more of these nuclei may be thrown off. In stained preparations, giant nuclei show a separation of the chromatin containing nuclear mass and the chromatin free portions; the latter form one or two round fluid-containing vesicular bodies which lie in the chromatin rosette.

Then the nucleoli increase in size, become vesicular, and take on a reticulated appearance. With the growth of the nucleolar bodies, the nuclear reticulum is pushed to the periphery and disappears. The remains of the chromatin rosette are condensed; if there are two nucleolar bodies, the chromatin lies between them, if only one, the chromatin mass is compressed at one side, giving the appearance of a signet-ring. Rarely, the chromatin rosette is absorbed during the growth of the nucleus, leaving the nucleolar body without a chromatin rosette. The nuclei may increase in size from the usual diameter of 10 to 14 μ to 70 or even 196 μ, and thus in a few days the nuclear mass may be increased by from 125 to 3,000 times. The fusion of nuclei plays no part in the production of giant nuclei. The chief cause is a growth of the nucleolar substance. Deep depression does not always end in giant nucleus formation; it occurs most often after depressions at the termination of which the *Actinosphæria* have been able to multiply for weeks and months. Hertwig regards the giant nucleus formation in *Actinosphærium* as the result of a series of changes which lead to the growth of the nuclei at the cost of the protoplasm. The growth of nuclei has, then, increased for so long, that finally their growth intensity renders a normal course of life processes impossible, and death results. The formation of giant nuclei would be favored, therefore, by excessive cell function.

3. Hyperplasia and hypertrophy of nuclei occurred in a depressed culture of *Actinosphæria,* containing a few animals with giant nuclei; most of the animals were of small or of medium size, with numerous pseudopodia and well defined cortex and medulla. These animals showed an enormously increased number of abnormally small nuclei (from one-half to three-fourths the normal size). Otherwise they had the usual structure of *Actinosphærium* nuclei. This condition coincided with a period of excessive feeding and

active multiplication, and during a whole month (April) the animals were characterized by the great number and the smallness of their nuclei.

This period was followed by one in which the nuclei were increased in size, with their chromatin divided into branching strands. These "hypertrophied" nuclei differ from the giant nuclei in their smaller size and in the absence of such great changes in the nuclear structure.

Besides the "hypertrophied" nuclei these *Actinosphæria* contain recently divided nuclei and nuclei of more or less normal size and structure. The "hypertrophied" nuclei are often oval in form and, in diameter, measure in the whole animal, from 21 to 35 μ, rarely 40 μ.

In some of these nuclei the chromatin is spread out over the whole nuclear network—hyperchromatic nuclei. In others, numerous chromatic nucleoli with short radiating processes lie on the reticulum. In the third type there are numerous sharply circumscribed vacuolated chromatic nucleoli. Transition stages are distinguishable, from nuclei with a few chromatic vesicles, to nuclei with a single large vacuolated nucleolus.

The nuclear framework varies from a fine webbed, delicate, granular network to one with coarse, homogeneous meshes. The nuclear meshwork is always sharply separated from the surrounding plasma by a membranelike thickening which is a further distinction between the "hypertrophied" and the "giant" nucleus.

Hertwig also describes chromatin-free nuclei, which usually contain a central achromatic nucleolus. The chromatin of these nuclei has degenerated and the nuclear framework becomes gradually shrunken.

The protoplasm of *Actinosphæria* with hypertrophied nuclei may be covered, in the living animal, with fat drops. In fixed and stained animals, it is purple or brown, owing to the presence of very finely divided chromatin. Chromidia are absent. Not infrequently, the nuclei are in sausage-like strings. Finally, it often happens that parts of such animals may become necrotic and be cast off as brown multinuclear masses.

Hertwig brings forward evidence to show that these "hypertrophied" nuclei may divide and may also play a part in the functions of the animal; they may also become reduced to small nuclei.

In these *Actinosphæria,* depressed by overfeeding over long periods of time, in cultures under observation for months, R. Hertwig has described a remarkable series of changes in structure, comprising shrinking, fusion and disappearance of pseudopodia, loss of distinction between cortex and medulla, chromidia and pigment formation, the presence of fat, the occurrence of areas of necrosis, the extrusion of nuclei, the degeneration of nuclei, as well as various modifications in the size, number and structure of the nuclei.

In these cultures there were periods of great depression, followed by intervals of regeneration of more or less great degree, as shown by return, more or less complete, to normal structure. Hertwig lays stress upon the fact that these various phenomena are associated with changes of the nuclear apparatus, the basis of which is "an increase of the nuclear substance at the expense of the protoplasm," a condition which occurs in connection with periods of excessive overfeeding and which must be referred to the increased capacity to assimilate food. Thus, both hyperplasia and hypertrophy of nuclei results from increased functional activity. According to Hertwig's ('04) view, the nuclear mass of a cell increases in amount by taking substances from the protoplasm, which has the power of splitting up substances suitable for the formation of secretions and which are taken up into the nucleus.

As long as the movement of substances from the protoplasm to the nucleus is in the ascendency, the existence of the nucleus is assured; while a preponderance in the passage of materials from the nuclei leads to a partial or total dissolution of these structures. The nuclear hypertrophy may be brought about by overgrowth or fusion of nuclei; and the increase of nucleolar substances is the chief factor in the enlargement of the nuclei.

It is evident that in these degenerative changes described by R. Hertwig in *Actinosphæria* depressed by overfeeding, the equilibrium between nuclear mass and protoplasm is markedly disturbed and that there must exist a struggle for ascendency between the two forces which under normal conditions work in coöperation.

This leads to his "Kernplasmarelation" theory, according to which, "for each cell there exists a definite size-relation of nuclear mass to cell mass, which may be represented by the formula K/P (nuclear mass divided by protoplasm mass)" ('03). As the variations of the "Kernplasmarelation" depend, above all, upon the assimilation capacity of the cell and upon cell division, he distinguishes a functional and a division growth of the nucleus. It is the functional growth of the nuclear mass which concerns us here. His studies on protozoa have led R. Hertwig ('03) to the conclusion that the "Kernplasmarelation" underlies not only periodic modifications brought about by the ordinary processes of life, but that under certain influences, it may experience more lasting changes.

These influences are: (1) uninterrupted function, (2) hunger, (3) change of temperature.

The marked effects of these influences upon the "Kernplasmarelation" Hertwig and his pupils have demonstrated by experiments not only upon *Actinosphærium, Paramœcium, Dileptus gigas* and *Frontonia,* but upon the egg cells of various metazoa.

Hertwig's view of the influence of temperature upon the "Kernplasmarelation," has been confirmed by the interesting work of H. Marcus ('06) on the fertilized eggs of *Strongylocentrotus lividus.* Marcus developed the eggs at 9° C., 19° C. and 22° C., and found that, in the blastula stage, the nuclei of those bred in the cold were distinctly larger in proportion to the protoplasm than of those bred at the higher temperatures.

Returning to *Actinosphærium,* it has been shown that the "Kernplasmarelation" is distinctly disturbed in hunger, in overfeeding and in encysting; in hunger by decrease in the protoplasm, in overfeeding by the functional increase of the nuclear mass; and in encysting by an increase on the part of the protoplasm of its property of dissolving nuclei.

SPECIAL PART.

The *Actinosphæria* upon which the following observations are based were taken by Professor Hertwig from his "B" culture at various times from February 4 until May 6, 1907.

Professor Hertwig furnishes me with the following notes of the culture, which was started in the fall of 1906 and continously overfed. "From the fourteenth to the thirty-first day of January there was enormous multiplication and feeding. The animals stopped feeding from January 31 till February 3, when feeding was resumed for a day, then there was no more feeding until February 11. On February 16 the animals were feeding enormously and there was much plasmogamy. On February 19 the culture showed many small food-free animals. After this there was heavy feeding, with increase in the size of the animals and plasmogamy until March 3. On March 11 and 13 they were feeding less. Then until March 27 there was enormous feeding, with clumping. From March 28 till April 3 there was decreased feeding.

"On April 6 the animals were in marked depression. On the eighth and eleventh day of April, they were feeding heavily again. Then, there followed a period of heavy feeding which lasted until April 25. On April 27 the animals stopped feeding and there occurred a period of marked depression, during which many of the animals died. There was no encysting. From May 1 to May 4 there was intermittent feeding. The culture died out on May 6."

The work assigned me was the accurate and detailed study of the changes present in animals taken at various stages of the culture by Professor Hertwig. These animals, with the exception of a few which were received alive, were fixed with picro-acetic and stained with boraxcarmine by Professor Hertwig, and given to me mounted in clove oil.

Descriptions and sketches were first made of the whole animals, which were then embedded in paraffin and sections cut at 7.5 μ. The conditions to which they were submitted were kept as uniform as possible.

For most of the organisms, the carmine stain was followed by either weak Delafield's hæmatoxylin, or by Heidenhain's iron hæmatoxylin. On the whole, the most satisfactory results were obtained in sections very lightly stained with Delafield's hæmatoxylin.

The material is best presented, perhaps, in groups arranged according to the months, from February to May inclusive, in which the animals were taken from the culture. In February, animals were taken on the fourth, ninth, eighteenth and twenty-sixth. During most of this time, the culture was in depression.

The first animal, received alive February 4, was of medium size, had a few very much thickened, blunt, short pseudopodia, and showed no demarcation between cortex and medulla, and no evidence of feeding. In stained preparations, studied both before and after sectioning, the cortex and medulla were fused, the spaces of the protoplasmic meshwork were small and thickened. The nuclei were very much increased in number, and somewhat in size (13.5 to 15 μ in diameter). The chromatin was in large irregular masses, usually connected by coarser or finer bands, forming rosettes and occasionally horse-shoe shaped forms. There were neither chromidia nor pigment. There was no evidence of nuclear fusion or of division. The second animal, which had on the fourth shown in the culture the same naked eye appearances of degeneration as the first, was killed on February 9. During this interval of five days it showed evidences of recovery (regeneration or restoration).

When killed it had short thick pseudopodia. In sections, the cortex was of normal width, well marked from the medulla, with a meshwork of normal size and appearance. The protoplasmic meshwork of the medulla was condensed and in the center of the animal it was thickened by the presence of a finely granular material. The nuclei were but slightly in excess of the normal number and were confined to the medulla. They were large—15 to 16.5 μ in diameter. The chromatic substance lay either in a single round or oval mass or in several round masses of unequal size, and near the center. The nuclear framework and nuclear membranes were distinct. Occasional degenerated nuclei without chromatin were seen. Some of the nucleoli were vacuolated. There was no fusion, division or overlapping of nuclei. A few scattered chromidia lay in the medulla, but there was absence of pigment. There was no evidence of feeding. This animal, compared with the first, showed distinct evidences of regeneration after a severe depression; it had developed pseudopodia, reëstablished its cortical layer, and reduced the number of its nuclei. It was abnormal, however, in having hyperplasia, hypertrophy and degeneration of nuclei.

On February 18 two animals were killed. They were both large, long, oval in shape, with a few short, thick, blunt pseudopodia. Sections of the larger of the two showed a fairly well-defined cortex of very irregular width, and a close, condensed alveolar meshwork, which was covered with fine granular plasma, and, at the extreme border, about the whole circumference, beset with fine yellowish brown pigment granules. The cortex contained no nuclei and no chromidia. The medulla, which contained two partly degenerated *Stentors,* was of a wide alveolar meshwork, which was covered, especially about the nuclei, with finely granular material and here and there with pigment granules. There were a moderate number of round, oval and irregular chromidia, lying, usually, about nuclei, and often connected with nuclear membranes.

The nuclei, which measured from 12 to 13.5 μ. in diameter, were considerably increased in number and were hyperchromatic. The chromatin was occasionally in round, solid, central masses, but in most nuclei it was scattered in large round or oval deeply staining masses, which were sometimes separated and sometimes connected by thinner branches of chromatic material. The nuclear meshwork was often obscured by these large masses. When visible, the nuclear meshwork was wide meshed and of uneven size. There was no vacuolization of nucleoli.

The other animal showed the same changes, except the chromidia were not so numerous. It contained no food material.

The last animal of this group was killed on February 26. It was actively feeding, of medium size, oval in outline, and without pseudopodia. The cortex was well defined from the medulla, and contained several large vacuoles. In the whole animal, the nuclei appeared very numerous and chromatin rich, while throughout the medulla great quantities of large and small, round, oval and irregularly shaped chromidial masses were present.

In sections the cortex was narrow and in places fused with the medulla. The meshwork was condensed, invaded by nuclei and beset with chromidia and a few pigment granules. The medullary meshwork was close set, the walls of the alveolar spaces thick and in many places crowded with chromidia. The latter appeared partly as fine masses, partly as large round, oval, or irregularly triangular branched masses. Here and there, also, it was in coarse vacuolated fibrils. These chromidial masses were often grouped about the nuclei and many were directly continuous with the chromatic substance of the nuclei.

The nuclei, which varied in diameter from 12 to 13.5 μ, were decidedly increased in number and were intensely hyperchromatic. There were two general types of nuclei; one, the most numerous, with the chromatic substance in large irregularly shaped masses connected by bridges of the same substance, the other, with the chromatic material scattered in small round or oval, irregular masses. The chromatic material, or nucleoli, rarely lay in the centers of the nuclei. The nuclear framework was fine and granular. The nuclear membranes were in general distinct, but, about some nuclei, they were absent in whole or part. The evidence that the chromidia arose from the nuclear chromatin was convincing, for a direct continuity between masses of intranuclear chromatin and these extranuclear chromatin bodies could be traced.

The second group comprised a series of eleven animals taken from the culture on the first, third, fourth, sixth, seventh, tenth, eleventh and thirteenth of March.

The animals of the first and third of March were of large size, feeding, with well-defined cortical layers, and rather numerous hyperchomatic nuclei of normal size. The first contained no chromidia and but little pigment. As Professor Hertwig suggested, this animal probably marked recovery after depression.

The two animals taken on March 4 were of medium size, not feeding and showed marked signs of depression, as evidenced by narrowing and condensation of the cortex, marked chromidia and pigment formation, and hyperplasia and hypertrophy of nuclei.

In sections the narrowed and thickened cortex was studded with fine refractile, yellowish brown pigment granules; the alveolar meshwork of the medulla was thickened by the presence of a homogeneous plasma and contained great numbers of chromidia and pigment granules. The nuclei varied from 10.5 to 16.5 μ in diameter, and were situated in the cortex as well as in the medulla. The chromatin was usually in the form of large irregular rosettes. The nuclear framework was distinct. About some of the nuclei the membranes were absent in whole or in part, with disintegration of the nuclear substance (see Fig. 14). Many nuclei touched at their borders, and overlapping of nuclei was frequent. Some of the large oval nuclei were evidently examples of fusion of two nuclei (see Fig. 3).

Chromidia were abundant and were usually grouped about the nuclei, and in many instances a direct continuity between them and nuclear chromatin could be traced (see Figs. 1 and 2). They occurred as small round or oval, large, irregular, vacuolated masses and as chromidial networks.

The organism was extremely rich in pigment, which was so thickly placed over one-fourth the body as completely to obscure the protoplasm. Over the rest of the animal, the pigment was in single, scattered or in clumped, granules. It was often in an intimate relation to the chromidia. In this animal pigment granules, identical in appearance with those in the plasma, were found in the nuclei. They were scattered over the nuclear meshwork near or on the chromatic substance, and were most often found in markedly hyperchromatic nuclei from which chromidia were projecting (see Figs. 1 and 2). The animal showed no evidence of feeding.

The three animals of March 6 are amongst the most interesting of the series. They all showed narrowing of the cortex, which was invaded by nuclei; there was hyperplasia, hypertrophy and hyperchromatism of the nuclei, marked chromidia and pigment formation, with condensation and thickening of the protoplasmic meshwork. In one of these animals, which showed the largest amount of chromidia of any of the series, the thickened, narrowed nucleus-containing cortex was beset with fine highly refractile yellowish brown pigment granules. The protoplasmic meshwork of the medulla was obscured in many areas by chromidia and pigment. The chromidia were enormously abundant and, frequently, were covered and surrounded by larger and smaller clumps of pigment granules (see Figs. 6 and 7). The nuclei, which were hypertrophied (from 13.5 to 15 μ in diameter), were remarkably hyperchromatic, and chromidia were pouring out from them in large quantities (see Figs. 4 and 7). Many nuclei contained pigment granules. Overlapping of neighboring nuclei (Fig. 4) was frequent, but no examples of true fusion of nuclei were observed. There were a few dissolving nuclei, with the nuclear membrane partly or completely absent and the chromatic material in small clumps. The animal was not feeding.

The animal of March 7, also not feeding, showed the same changes described for those of March 6. The pigment was even more abundant, the granules being not only scattered over the protoplasmic meshwork and about the nuclei, but often occurring in large clumps, usually in a nest of disintegrating chromidia.

Many nuclei contained pigment granules. Vacuolization of the nucleoli was common. Two other forms of nuclear degeneration were noted, shrivelling of nuclei and disintegration of the nuclear membrane, in whole or in part, with the escape of the nuclear contents into the protoplasm. Several striking examples of nuclear fusion were observed (Fig. 3).

The animals of March 10 and 11 were of medium size, not feeding and contained no chromidia; only one showed pigment. There was nuclear hyperplasia, hypertrophy and hyperchromatism. The nuclei varied from 15 to 18 μ in diameter. Touching, overlapping and apparent fusion of nuclei were common.

The last animal of the series, killed March 13, was comparatively small, and had a few short thick pseudopodia and a very thin and narrow meshed cortex. The nuclei were smaller and less numerous than in the other animals of this series. The nuclei were confined to the medulla and were not hyperchromatic. There were a moderate number of chromidia and no pigment. The animal was not feeding.

The third group consisted of a series of twelve animals killed on sixth, seventh, eighth, tenth, and eleventh of April. They were, with two exceptions, small.

Two animals were killed on April 6. The first was of medium size, contained no pigment and no food. The demarcation between medulla and cortex was distinct. The meshwork of the latter was wide and contained well marked vacuoles. The protoplasmic meshwork of the medulla was of normal size, except in the center, where it was condensed. The meshwork, especially in this central area and about the nuclei, was covered with homogeneous or very finely granular achromatic material. A few small round or oval chromidia were about some of the nuclei. In the spaces of the protoplasmic meshwork, there were large numbers of free vacuolated nucleoli (Fig. 10), from ten to fifteen being counted in a single section.

The nuclei were markedly increased in number, but were remarkably small, measuring from 7.5 to 10.5 μ in diameter. They were often crowded together in clumps, of two, three, four or more, their membranes touching over a small area. Overlapping of nuclei was common (Figs. 8 and 9). There was no fusion of nuclei and no division figures were to be found. The nuclei varied markedly in their chromatin content, some being markedly hyper- and others markedly hypochromatic. In the former the chromatic material was usually in irregularly shaped branching rosettes and was often beset with one or more large or small vacuoles. In the latter, the chromatic substance was usually in small round or oval scattered masses, often near the nuclear membrane. In some of these hypochromatic nuclei, the chromatin lay partly within and partly without the nuclear membrane. In one such nucleus, the nuclear membrane was lacking for about one-fourth the circumference. Some nuclei contained no chromatin and others only a few fine particles.

A common change in the nucleoli was vacuolization, which affected small as well as large chromatin masses. In the large nucleoli, the vacuoles were large and ring-shaped, and frequently a number of smaller vacuoles were grouped about a large central vacuole. In many nuclei, large vacuolated nucleoli were separated from the achromatic substance and in various stages of extrusion. Some of these bodies lay just outside the nuclear membrane. It is possible that these appearances were mechanically produced by the microtome knife.

Undoubtedly the most common change by which the large vacuolated nucleoli were set free in the protoplasm was by the dissolution of the nuclear membrane and the achromatic nuclear material. All the steps of this process could be readily traced.

Another set of changes which led to the presence of large vacuolated masses in the protoplasm, was seen best in sections stained with iron hæmatoxylin. This change was characterized by shrivelling and condensation of the nuclei, with the accumulation of the chromatic material about the condensed nuclear membrane, and by hyaline degeneration and vacuolization of the achromatic nuclear material. The vacuolated body resulting from these changes could be distinguished from the typical, free lying, vacuolated nucleoli, by the presence in the former of a group of smaller vacuoles or of hyaline nuclear substance lying within the chromatic ring (see Figs. 17 and 18). In the typical vacuolated nucleoli, the vacuoles appeared as empty spaces in the chromatic substance. Fig. 18 shows an interesting example of hyaline degeneration of the nuclear framework.

The second animal showed the same changes described in the first. The only special difference between the two animals was the greater number of nuclei and the smaller number of free vacuolated nucleoli in the second.

This animal was infested with great numbers of small (8.25 to 11.25 μ in diameter) closely packed, hyperchromatic nuclei. They showed to a less marked degree the same changes described in the first. The animal showed no evidences of feeding.

On April 7, two medium sized animals which were fused over a portion of their cortices were killed. They both contained small food vacuoles, were without pseudopodia and had narrow but distinct cortices, the meshwork of which was small but not specially thickened. In sections they were nearly identical in structure. The protoplasmic meshwork of the medulla was relatively wide, except in the center where it was condensed. In general it was covered with finely granular, achromatic material. There was entire absence of both pigment and chromidia. The nuclei were very numerous and relatively small, varying from 8.25 to 11.25 μ in diameter. They were, for the most part, hyperchromatic, the chromatic material being usually in large masses or rosettes. Nuclei with finely divided chromatic material were uncommon. In most nuclei the chromatic material was vacuolated. Some showed the large vacuolated chromatic nucleoli described in the animals of April 6 (see Fig. 11). In general, the nuclear framework and membranes were distinct. There were a number of nuclei in various stages of dissolution, with loss of the nuclear membrane and disintegration of the reticulum, as described in previous animals; such nuclei had vacuolated nucleoli, and this was evidently one of the processes leading to the presence of vacuolated nuclei in the plasma. Another change resulting in such free vacuolated nucleoli was the shrinkage and concentration of nuclei in association with hyaline change of the nuclear framework, as previously described. The result was the formation of hollow, spherical or bizarre shaped shells of deeply staining chromatic material, enclosing one or more large vacuolar spaces and sometimes studded with smaller vacuoles (see Figs. 19 to 25). One of these masses of vacuolated nucleolar material measured 25 μ in length (giant vacuolated nucleolus, see Fig. 25). A common shape for the smaller masses was that of a signet-ring. Some of these free vacuolated bodies were evidently due to the extrusion of a vacuolated nucleolus before disintegration of the rest of the nucleus.

The three animals of April 8 were small, but actively feeding. Two had a few short blunt pseudopodia. The cortex was narrow but well defined from the medulla. They contained no chromidia, pigment, or free vacuolated nucleoli. The nuclei were distinctly, though not greatly, increased in number, and were hyperchromatic. They varied from 9 to 13.5 μ in diameter. The nuclear chromatin was arranged either in large loosely formed rosettes or in small scattered masses. There were no evidences of nuclear division, fusion or dissolution.

On April 10, three more animals were killed. They were all actively feeding and had a few short, stout, blunt pseudopodia. Their protoplasm was of normal structure and contained neither chromidia nor pigment. The nuclei were distinctly over-numerous and were hyperchromatic. They varied widely in size (from 9 to 15 μ in diameter); the smaller type of nuclei outnumbered the large.

Of the animals killed on April 11, two agreed in all respects with those of the tenth. The third had a distinctly increased number of large (15 to 18 μ in diameter) hyperchromatic nuclei. The nucleoli were often vacuolated.

The last group consisted of ten animals which were killed between the first and the sixth of May.

Three animals killed May 1 were small, round, actively feeding, and had a few short twisted pseudopodia, a well defined and developed cortical layer containing large vacuoles. The medullary meshwork was of unequal size and beset with large and small chromidia, which often showed vacuolization. The over-numerous and vacuolated hyperchromatic nuclei varied from 10.5 to 13.5 μ in diameter. There was no evidence of fusion, division or dissolution of nuclei. Pigment was absent in two. In one animal which was especially rich in chromidia, the latter were usually covered and always surrounded by innumerable, very fine dust-like particles of chromatic material, which obscured the protoplasmic meshwork. This deeply staining "chromatin dust" was quite distinct from the highly refractile yellowish brown pigment granules, which were also present in small numbers.

The animals of May 2, 3 and 4 were in all respects similar to those of May 1.

The animal killed on May 5 was shrivelled and distorted in shape. The abnormally wide cortex contained large irregular vacuolar spaces, separated by a coarse protoplasmic framework. The outer layer of the cortex was covered over wide areas with a deeply staining homogeneous material—dissolved chromatin.

The relatively small medulla consisted of a very wide and irregular sized meshwork, the coarse strands of which were covered with finely granular achromatic material and with "chromatin dust." There was a considerable number of large and small chromidia, but no pigment. The nuclei were hyperchromatic, with a coarse reticulum and vacuolization of the nucleoli. The nuclei measured 12 μ in diameter.

The last animal of the group and of the study, for the culture died out on this day, was killed on May 6. It presented a very peculiar appearance. In the whole animal, the outlines were very irregular and no separation between cortex and medulla could be discerned. When stained with borax-carmine, the animal presented a granular non-staining outer layer and an inner irregularly shaped, granular diffusely staining mass, which formed the bulk of the organism. In sections, there was no distinction between cortex and medulla and the protoplasm was obscured by the presence of dissolved chromatin and large vacuolated chromidia. Only an occasional nucleus could be found. One which was measured had a diameter of 10.5 μ.

The progress and interrelations of the various changes observed in these "depressed" *Actinosphæria,* the methods adopted by the animals to readjust themselves and the successive stages in the finally unsuccessful struggle can be, perhaps, presented best by contrasting the appearances met with in the various groups.

The culture sprung from *Actinosphæria* which had been caught at the beginning of winter. The animals at that time showed to a high degree the capacity for encysting, which was gradually lost, so that animals exposed to warmth no longer formed normal cysts. Some of the animals perished at this time from the formation of giant nuclei. My material sprang from animals which had survived this period.

The animals of February and March, after a prolonged and only occasionally interrupted period of overfeeding, showed profound depression, marked at times by distinct and often well marked signs of restoration. Their protoplasm was degenerated to a more or less marked degree. There was a variable amount of nuclear hyperplasia, hypertrophy and hyperchromatism. The animal of February 26 and most of those in March showed large amounts of chromidia and often pigmentation. Throughout, there was dissolution of nuclei, and, in the later animals, fusion and shrivelling of nuclei, and often vacuolization of nucleoli.

In the April group, after another period of heavy feeding, the animals were in almost all respects, except for some of the modes of nuclear degeneration, quite different from those of the previous series. The chief characteristics of the animals of April 6 and 7 were the great number of relatively small nuclei (from 7.5 to 10.5 μ and 8.25 to 11.5 μ in diameter) and the occurrence of shrinkage, hyaline degeneration, and dissolution of nuclei, with the vacuolization of nucleoli, rather than the formation of chromidia, as the modes of reduction of excessive nuclear substances.

That these degenerative methods of reduction of nuclear substances may be effective is shown by the great differences presented by the remaining animals of this group. With few exceptions they were feeding actively; their nuclei, while usually over-numerous, were greatly reduced in number, and the general appearance of the animals was less abnormal. The nuclei were, however, both hypertrophied and hyperchromatic, due probably to the heavy over-feeding. In the last animal of the April group the nuclei reached a diameter of 18 μ.

From the eleventh to the twenty-fifth of April the culture fed heavily, and on the twenty-seventh the animals were again markedly depressed.

The animals taken on the first two days of May were feeding, the cortical layers were fairly well developed. The nuclei were of full size (10.5 to 13.5 μ in diameter), decidedly hyperchromatic and over-numerous. The nucleoli were often vacuolated, but dissolution of nuclei and free nucleoli were not seen. There were, however, enormous numbers of chromidia and much "chromatin dust." Some of the animals contained pigment.

The animals of May 3 and 4 were small, without food, and had relatively large nuclei and a somewhat smaller number of chromidia.

The animal on May 5 was shrivelled and distorted, with relatively little medulla, and the cortex contained a considerable amount of homogeneous dissolved chromatin. Otherwise it resembled those of the two previous days.

In the animal of May 6, the protoplasm was markedly degenerated and distorted, and but few nuclei could be recognized.

Reviewing the whole material, it is seen that, during the entire period covered by these observations, the animals showed not only a hyperplasia of nuclear substances, but evidences of profound changes in the structure of the protoplasm. It will be noted that typical giant nuclei were not present (the period for this having passed) and that the hypertrophied nuclei of this culture did not reach the extreme size obtained by those of Professor Hertwig's 1902 culture. I have designated as "hypertrophied nuclei" those nuclei which exceeded the extreme limit (14 μ) which he gives for normal nuclei. While there were times when the nuclear mass was reduced considerably and when the protoplasm approached its normal structure, organisms with normal nuclei in normal protoplasm were not observed; the "Kernplasmarelation" was never reëstablished, and complete recovery did not occur.

With the exception of giant nuclei, the necrosis of parts of protoplasm, fat and the transformation of all the nuclei to chromidia, all the nuclear and protoplasmic changes described by R. Hertwig ('04) in *Actinosphæria* depressed by overfeeding and prolonged culture, were observed in the series of animals described in the present communication. In regard to the absence of fat, it should be stated that most of the animals had been fixed and stained (and therefore treated with alcohol) before they were received by me.

In addition to confirming R. Hertwig's previous observations in most particulars, three new points were established in regard to *Actinosphæria* depressed by prolonged overfeeding, namely, the occurrence of pigment granules in hyperchromatic nuclei; hyaline degeneration of the nuclear reticulum leading to the formation of shrunken, vacuolated nuclei which in some respects resemble the free vacuolated nucleoli of R. Hertwig; and, finally, the fact that in *Actinosphæria* with large hyperchromatic nuclei, the reduction of nuclear mass is accomplished mainly by the extrusion of nucleolar substance and chromatin as chromidia (chromidiosis), while in animals with great numbers of relatively small nuclei, this is effected chiefly by shrinking, dissolution and various other degenerations of nuclei.

GENERAL PART.

It remains now to interpret these various nuclear and protoplasmic changes in the light of recent knowledge and to point out their relation to certain aspects of the general physiology and pathology of the cell.

In regard to the increase of the nuclear mass, it was both actual and relative. With R. Hertwig ('04) I can recognize three forms of increase of the nuclear mass, (1) the enlargement of single nuclei, (2) increase in the number of nuclei and (3) increase in the number and size of nuclei.

As previously stated, in the present series of *Actinosphæria* the time for the formation of giant nuclei was passed and the hypertrophied nuclei did not reach the size attained in Professor Hertwig's 1902 culture—21 to 35 μ. One possible explanation is that most of my measurements were made of nuclei in sections, which had been treated with xylol. Some of the nuclei exceeded 18 μ in diameter. All of the animals, however, had an excess of nuclear material, in the shape of either a markedly excessive number of small or large nuclei or of a less marked excess of large nuclei. The protoplasm, whether of large or of small animals, always showed more or less well marked structural changes and was relatively small in proportion to the nuclear mass.

R. Hertwig has pointed out that this increase in the nuclear mass must be due to increased functional activity associated with the continuous overfeeding and the resulting overnutrition. He has suggested the same explanation for the large nuclei of carcinoma and sarcoma cells and of certain cells in inflammatory processes.

The nuclear hyperplasia in depressed *Actinosphæria* must, of course, be effected by mitosis, and it is not unlikely that the functional growth (hypertrophy) may produce in R. Hertwig's sense sufficient " Kernplasma tension " to start nuclear division. There is absolutely no evidence that the chromidia of depressed *Actinosphæria* ever give rise to new nuclei corresponding to the secondary nuclei of the Thalamorphora arising from the " Chromidialnetz."

R. Hertwig ('04) regards the occurrence of nuclear hyperplasia in depressed *Actinosphæria* as a good sign, for such animals may assimilate and multiply enormously, while most giant nuclear animals die. The division of the nuclear materials into multiple small masses would, he thinks, afford better conditions for carrying on the life processes.

The formation of chromidia and most, if not all, of the various forms of nuclear degeneration described in these animals, are to be looked upon as the results of the use of physiological means, for, to a considerable degree, the same processes occur in encysting *Actinosphæria,* in which the number of the nuclei is reduced normally to an astonishing extent. Chromidia may occur in normal animals and in the encysting process a great number of chromidia are extruded from the nuclei in the cysts, though most of the reduction in the number of nuclei occurring before encysting is accomplished by absorption of nuclei rather than by dissolution into chromidia. As in the processes leading up to encysting, so in these depressed animals, abnormally stocked with nuclear materials, the protoplasm exerts its power of destroying the nuclei in order to reëstablish the "Kernplasmarelation."

I have stated already, that there is no evidence that the chromidia of depressed *Actinosphæria* possess a propagatory function in the sense of Schaudinn and Goldschmidt ('04), *i. e.,* they do not form new nuclei. According to Goldschmidt's ('04) interesting theory, these chromidia represent excessive somatic chromatin needed and used by the animals to assist in the active function which they are carrying on.

Against this view are the facts that the greatest number of chromidia are not present in the more actively feeding animals and that the chromidia break up into pigment. In favor of his theory, however, is the fact that, when the nuclei are large and relatively less numerous in feeding depressed *Actinosphæria,* chromidia are much more plentiful than in animals with great numbers of small nuclei. That normal *Actinosphæria* form chromidia during functional activity cannot be denied. It is possible that in depressed *Actinosphæria* the existence of two kinds of chromidia is to be recognized, one highly functioning, somatic in type, and the other formed in the efforts of the animal to reduce its surplus of nuclear substances and destined to be got rid of.

The formation of pigment from nuclear material is of great interest. R. Hertwig ('02) first suggested that the pigment of melano-sarcoma cells is formed from chromatin extruded from the nucleus in an effort of the cell to reduce its nuclear mass and thus to reorganize itself. Later ('04) he described the transformation of chromidia to pigment and recognized the possibility of the development of pigment from the nucleus, and called attention to the fact that the two agents (cellular activity and cold) which best effect relative enlargement of the nuclear mass also produce conditions most favorable for pigment formation. He referred, of course, to autochtonous iron free pigment.

R. Hertwig's pupil Roessle ('05) has traced, in the cells of melano-sarcoma, the wandering of nucleolar substance from nuclei over-rich in this material and its transformation into pigment in the protoplasm. Roessle suggested that the pigment formation of senile atrophy, probably partly physiological and partly pathological, is produced in the same way as the pigment of *Actinosphærium* and showed that, as far as micro-chemical methods go, the pigments of *Actinosphærium,* melano-sarcoma and brown atrophy appear to be identical, and are iron free. Meirowitz-Grandenz ('07), studying pigment formation in the skin after exposure to the Finsen light, was able to trace the development of pigment from nucleolar substance, both in the nucleus and in the protoplasm. The same processes were evident in the *Actinosphæria* described by me.

Through the courtesy of my friend, Dr. H. Marcus, I have observed pigment granules in the nuclei of pigmented epidermal cells in his sections of Professor Brauer's *Hypogeophis rostratus* material.

The nuclear degenerations present in these *Actinosphæria* have much in common with those which occur in various pathological processes in the higher animals, and, as R. Hertwig has shown, bear a striking similarity to some of the nuclear degenerations described by Pianese in carcinoma and erroneously interpreted as parasites by various authors. This is especially true of the vacuolization of nucleoli and the hyaline degeneration of nuclei met with in the present series of animals.

The condition of the protoplasm in many of these overfed *Actinosphæria* was as abnormal as that of the nuclei. There was loss or degeneration of pseudopodia, fusion of cortex and medulla, loss of vacuoles, condensation and shrivelling of the protoplasmic meshwork, and, in R. Hertwig's previous series, necrosis of protoplasm and the presence of fat. To what causes are these changes to be assigned? In the present state of our knowledge it is impossible to explain them satisfactorily. It seems, probable, however, that the exhaustion of overwork in digestion and in breaking down nuclei, the loss of materials to the ever-growing nuclei and the intoxication from retained metabolic products are among the factors concerned.

In conclusion, I take this opportunity to express my heartiest thanks to Professor Hertwig, not only for his material, his supervision and many suggestions in this work, but for many kindnesses extended to me in his institute.

MUNICH, May 22, 1907.

EXPLANATION OF PLATES XVI–XIX.

The drawings were made with the aid of a camera lucida, under Leitz 1/12 oil immersion objective, ocular 3, tube length 160 mm.

FIGS. 1 and 2. Hyperchromatic nuclei giving off chromidia, containing pigment granules, and surrounded by chromidia and pigment. Animal of March 4.

FIG. 3. Hyperchromatic nuclei; fusion of two nuclei. Animal of March 7.

FIG. 4. Small portion of periphery of animal of March 6. Note fusion of cortex and medulla, overlapping of nuclei, chromidia and pigment.

FIG. 5. Large hyperchromatic nucleus, probably the result of fusion of two nuclei. Animal of March 3.

FIG. 6. Condensation of protoplasm, intense chromidiosis, with large central clump of pigment granules.

FIG. 7. A large nucleus surrounded by chromidia and pigment granules.

FIG. 8. Small area of medulla of animal of April 6, showing marked nuclear hyperplasia. Note that the nuclei are small and touch at their borders.

FIG. 9. Overlapping of two small nuclei. Animal of April 6.

FIG. 10. A free vacuolated nucleolus between two small nuclei. Animal of April 6.

FIGS. 11 and 12. Nuclei with vacuolated nucleoli. Animals of April 6 and 7.

FIGS. 13 and 14. Stages of dissolution of nucleoli. Animals of March 4 and April 7.

FIGS. 15 and 16. Shrunken nuclei. Animals of March 4 and April 6.

FIGS. 17 and 18. Hyaline degeneration and vacuolization of nuclei. Animals of April 6 and 7.

FIGS. 19 to 25. Types of vacuolated nucleoli lying free in the protoplasm. Animal of April 7.

All the photographs (Figs. 26–28) are taken at the same magnification = × 100.

FIG. 26. Photograph of section of normal *Actinosphærium.* Note the wide cortex and the number and distribution of the nuclei.

FIG. 27. Photograph of section of a depressed *Actinosphærium.* Note hyperplasia, hypertrophy and hyperchromatism of the nuclei, condensation of the protoplasmic meshwork and the presence of chromidia. Animal of March 6.

FIG. 28. Photograph of section of a depressed *Actinosphærium* during a period of active overfeeding. Note the numerous vacuoles and marked hyperplasia and hyperchromatism of the nuclei. Animal of April 7.

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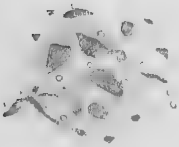

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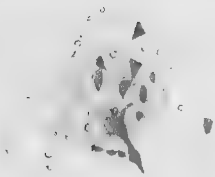

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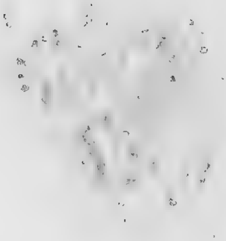

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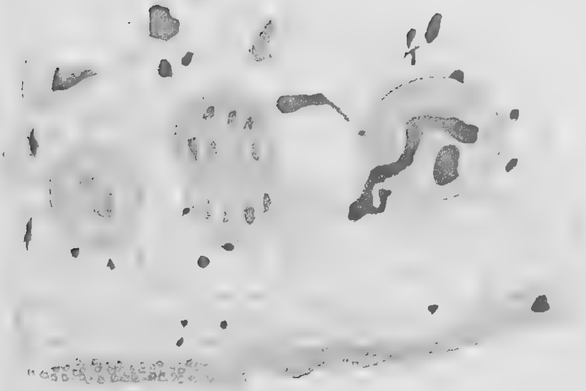

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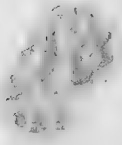

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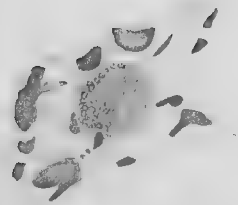

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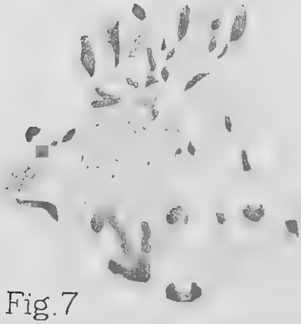

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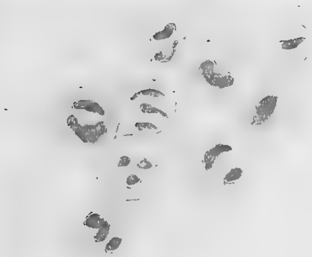

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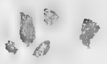

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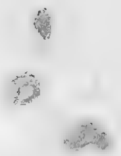

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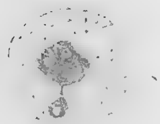

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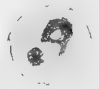

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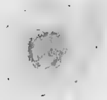

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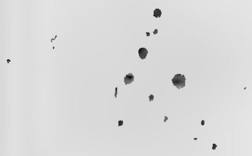

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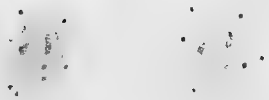

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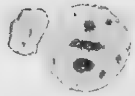

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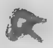

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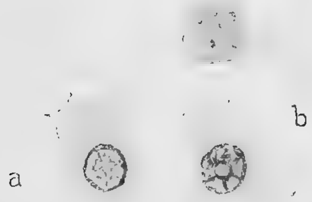

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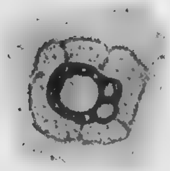

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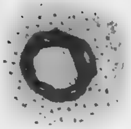

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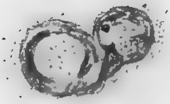

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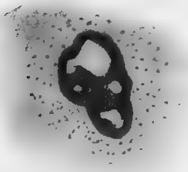

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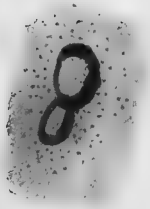

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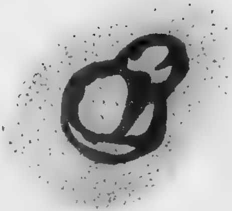

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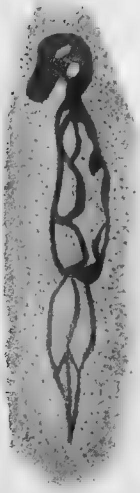

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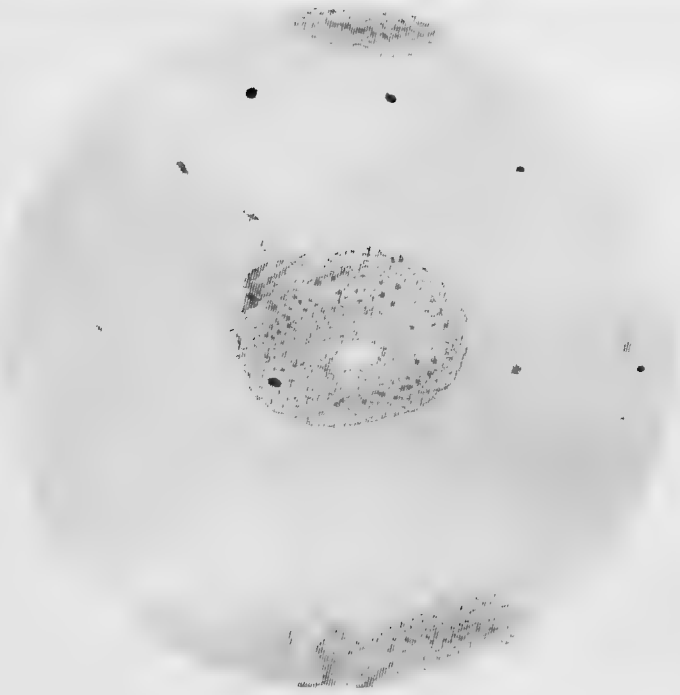

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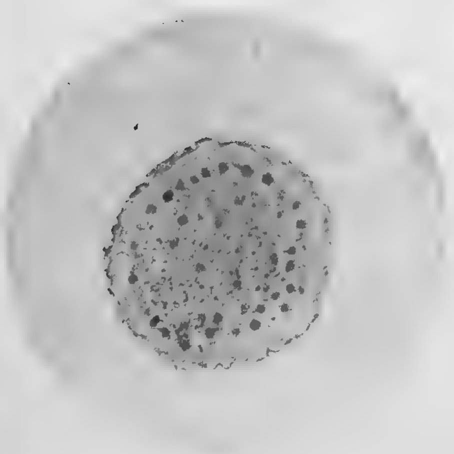

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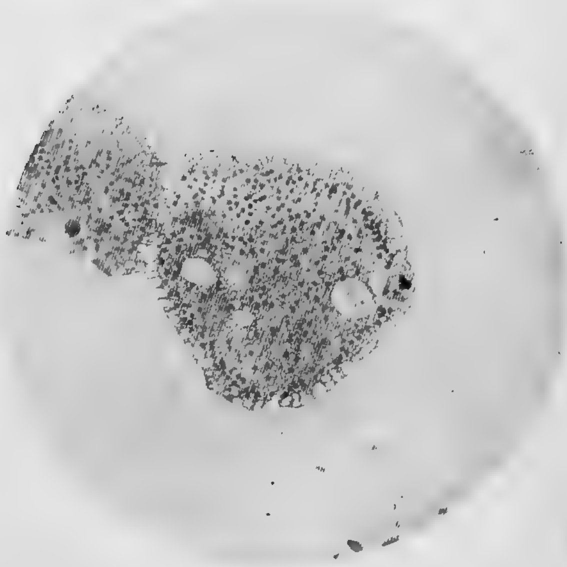

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AN EXPERIMENTAL STUDY ON HEMORRHAGE FOLLOWING SECTION OF THE UTERINE AND OVARIAN VESSELS IN DOGS AND ITS POSSIBLE BEARING ON RUPTURED PREGNANCIES.*

BY

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(With illustrations.)

PHYSIOLOGISTS have estimated the total quantity of blood in the human body at about 7.7 per cent. of the body-weight. Thus, a woman weighing 130 pounds would have a blood content of about ten pounds.

Now "just what percentage of loss"—to quote from Howell—can be borne by the human being has not been determined, but it is probable that a healthy individual may recover without serious difficulty from the loss of a quantity of blood amounting to as much as 3 per cent. of the body-weight." This, in a woman of 130 pounds, would be a loss of four pounds, or approximately 1,650 c.c. We question whether so large an amount or, at any rate, much more blood is found in the average patient of the above weight as a result of the hemorrhage resulting from a ruptured ectopic gestation.

During the past nineteen months we have been conducting a series of experiments on dogs to see if it might not be possible to throw some light on this phase of the subject from the standpoint of hemorrhage.

These experiments, so far as we have gone, (thirty-one exper-

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*Read before the American Gynecological Society, at Philadelphia, May 26 to 28, 1908.

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iments) seem to show that, in dogs at least, hemorrhage from large internal vessels ceases before it is sufficient to prove fatal. No dog succumbed to the hemorrhage following excision of the ovary, division of the broad ligament with section of the left uterine vessels, section of the uterine vessels on both sides and other lesions. In none of these cases did the dog succumb to the hemorrhage although we probably subjected our animals to as great a risk of bleeding to death as is incurred by the average woman suffering from a ruptured tubal pregnancy.

Before taking up in some detail the findings in our experimental work I would like to briefly recall to your memory the anatomy of the parts. In the bitch the uterus consists of the body or corpus and its two long horns or oviducts; in the latter fetal development takes place. The oviducts are connected anteriorly with the very short, slender Fallopian tubes; the outer ends of the latter lie very near the ovaries, which are situated posterior and dorsal to the kidneys. Each uterine artery is a branch of the pudic, the latter being one of the two main divisions of the internal iliac; they are vessels of considerable size, even as compared with the corresponding arteries in women. The ovarian vessels, on the other hand, are quite small. (V. Figs. 1 and 2.)

With these anatomical differences in mind, a résumé of the cases is herewith presented:

The experiments carried out may be divided into the following series:

1. Division of the uterine and ovarian vessels.
2. Division of the uterine vessels producing shock. Secondary operation on dog while in a condition of shock.
3. Division of the uterine vessels and observations on the blood-pressure and hemoglobin.
4. Division of the uterine vessels and observation on the pulse, respiration and hemoglobin with special reference to the time of the clotting of the blood.
5. Division of the vessels, observations on the pulse, respiration and hemoglobin before and after bandaging and before and after applying weights to the lower abdomen.
6. Division of the uterine vessels with the dog in the upright position; observations on the pulse, respiration and hemoglobin.

EXPERIMENTS.

Series No. 1. Division of the Uterine and Ovarian Vessels.

In this series we have carried out excision of the ovary, divi-

EXPLANATION OF PLATES.

The diagrams afford a comparison between the uterine artery in the human being and that in the dog. FIG. I, which shows the artery in the human subject, is a composite picture of the diagrams in Corning's and Gray's Anatomies. FIG. II, which shows the distribution of the uterine and ovarian arteries in the dog, was made after injecting the blood-vessels.

It will be seen that in the human being, at the points at which the uterine comes off from the anterior branch of the internal iliac, there is a much sharper angle than in the dog.

In order to show the course of the uterine artery in the dog the uterus with the oviducts was placed over the symphysis pubis.

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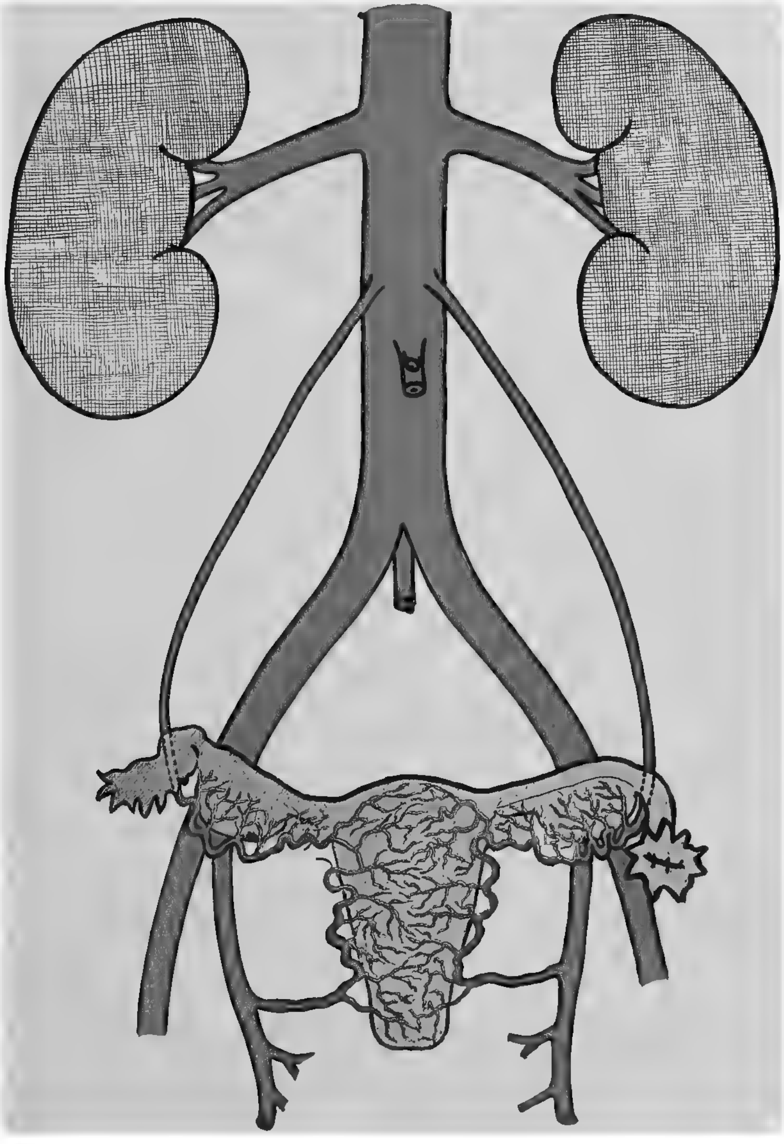

Diagram of the Distribution of Uterine and Ovarian Arteries in the Human Subject.—*Robb.*

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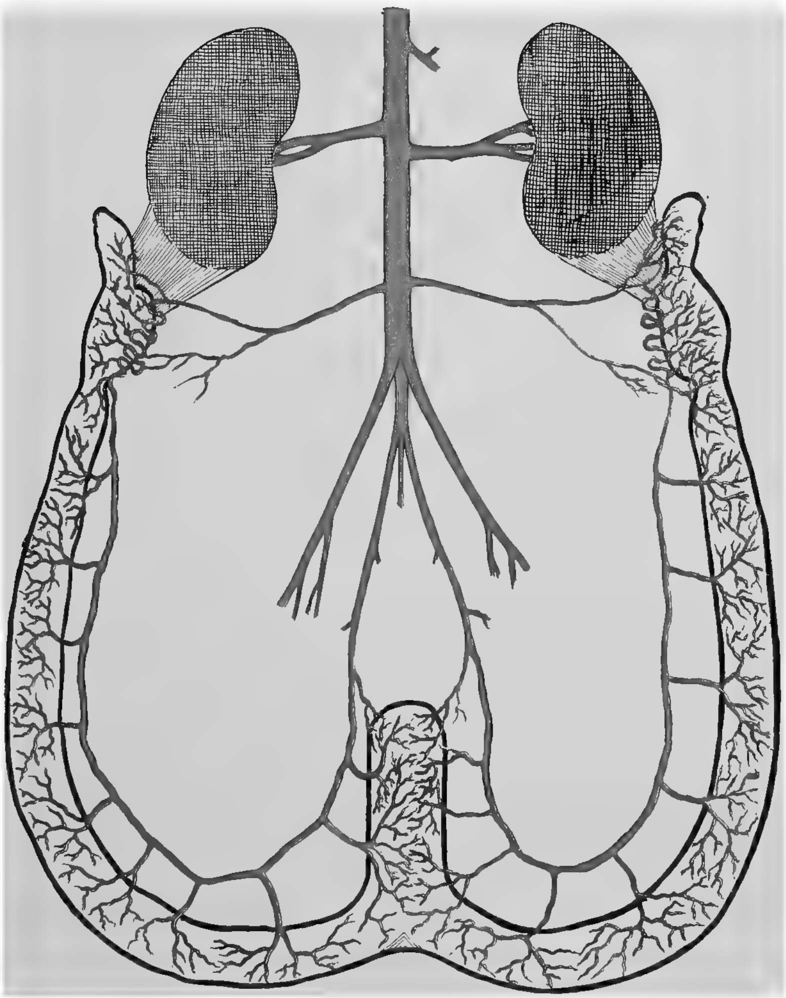

DIAGRAM OF THE DISTRIBUTION OF UTERINE AND OVARIAN ARTERIES IN THE DOG.—*Robb.*

sion of the broad ligament with section of the left uterine vessels, section of the uterine vessels on both sides and other lesions. In none of these cases did the dog succumb to the hemorrhage.

Dog No. 1.—Well nourished. Weight 6.5 kilos.

January 11, 1907. Ether anesthesia. The abdomen was opened through a median incision 6–7 cm. long. Pelvic organs apparently normal. The outer end of the right oviduct was cut through, and the right ovary excised. There was no free bleeding at the site of the injury. The incision was closed in layers. There was but little variation in the pulse throughout the operation. Quick recovery from ether and an uneventful convalescence.

Dog No. 2.—Well nourished. Weight about 12 kilos.

January 25, 1907. Ether anesthesia. Median incision 4 cm. long. Pelvic organs apparently normal. The right broad ligament was cut through its entire extent, the uterine vessels being severed. There was active arterial hemorrhage, the blood welling up into the abdominal wound. Incision quickly closed in layers. At the end of the operation the mucous membranes showed a distinct blanching. Pulse 140, of small size. Dog conscious thirty minutes after being put to bed. A good deal of vomiting during first six hours.

January 26. Dog is up and walking about, showing no signs of pain. This dog escaped from her cage several days later. She had made a good recovery , so far as we could judge.

Dog No. 3.—Good condition. Weight about 10 kilos. "In heat."

January 30. Ether anesthesia. Median incision 4 cm. long. Pelvic organs congested. Outer end of left oviduct cut through and left ovary excised. The left uterine vessels were now cut across. Free bleeding from the latter and also from the ovarian. Incision quickly closed in layers. At end of operation pulse of rather small volume, rate not obtained. Dog conscious soon afterward.

February 2. Condition good. Dog disposed to remain quiet.

February 6. Dog bright and active, taking her food well.

Dog. No. 4.—Well nourished. Weight about 10 kilos.

February 2. Ether anesthesia. Median incision 4 cm. long. Pelvic organs normal. The uterine vessels on both sides were cut across. Very free bleeding. Incision quickly closed in layers. Pulse rapid, but of fairly good volume. Dog conscious before leaving the table. Given morphine gr. $\frac{1}{3}$ hypodermically at once. Thirty minutes later dog was standing and drinking water greedily.

February 6. Dog suffered apparently but little from operation. To-day seems bright but is not disposed to move about much.

February 16. Dog made an uninterrupted recovery.

Dog No. 5.—Feb. 6. In good condition. Weight about 10 kilos. Normal pelvic organs. The left ovary was excised, and the uterine vessels on both sides were cut. There was the usual free hemorrhage. Immediate closure in layers. Dog conscious on reaching bed. Pulse not very rapid and of good volume. Seen thirty minutes later, dog had changed position, but was then perfectly quiet.

February 9. Dog had been doing well. Yesterday was eating. To-day does not appear so bright. Does not object to being moved. Pulse and temperature normal.

February 16. Rapid improvement since last note. Dog now active.

Dog No. 6.—This is the same animal used in Experiment No. 1 (q.v.).

February 9. Dog had made a complete recovery from first operation. Ether anesthesia. Abdomen reopened through former incision. No free fluid or clotted blood found in peritoneal cavity. A few delicate adhesions about the pelvic structures. The right oviduct was enlarged and bent upon itself. In the left oviduct were two fusiform swellings, the one about 1.5 cm. from the corpus uteri, the size of a pigeon's egg; the other in the outer half of the oviduct, almost as large as a duck's egg, apparently filled with clear fluid. The uterus and oviducts were now removed *in toto* by one continuous cut of the scissors from side to side. Bleeding was profuse. Immediate closure in layers. At end of operation pulse hard to obtain; respirations shallow. Dog able to open her eyes. Seen fifteen minutes later dog was standing on all fours, lapping water.

February 16. Dog did not appear to be suffering from operation. A few hours afterward was walking about in her cage. No sedative was given. At present seems to be in good condition.

February 25. Dog has apparently made her second complete recovery. Incision well healed.

Dog No. 7.—Same animal as No. 3 (q.v.). The first operation had been made seventeen days before. The left ovarian and uterine vessels were cut. Dog has made complete recovery. Now bright and lively.

February 16. Ether anesthesia. Abdomen reopened through former incision. No blood found in peritoneal cavity. A few light omental adhesions. No pulsation could be detected in the stump of the left uterine artery, nor was there any clot around it. The right uterine vessels were now cut, and temporary closure of the abdominal cavity was made by placing clamps on the edges of the divided peritoneum. At the beginning of the operation the pulse-rate was 128. The dog was now kept under a light anesthesia. Fifty minutes after cutting of vessels the pulse began to show an increased rate, being at this time 136. A steady rise continued during the next thirty minutes, at the end of which time the rate was 156. The clamps were now removed from the peritoneum, and the blood found in the pelvis was carefully removed with gauze sponges. After gentle application with a gauze sponge at the cut end of the artery cessation of the bleeding resulted at the end of about ten minutes. Twenty minutes later a subcutaneous infusion of salt solution (400 c.c.)

was given. This was nearly all taken up in thirty minutes. It was given to see if the subsequent rise in the blood-pressure would bring on a recurrence of hemorrhage from the uterine artery. No such effect was produced at the end of thirty minutes after the absorption of the saline solution. Gentle squeezing of the end of the vessel, however, was sufficient to expel the clot, which had formed, and fresh bleeding began. The experiment was brought to a close at this point, the uterine artery ligated, and the incision closed in layers at once. The pulse-rate at the end of 3½ hours consumed in the observation was 144.

February 25. Dog has done well from day of operation. Is now as active as ever. The amount of blood lost during the experiment was estimated approximately and found to be 240 c.c.

Dog No. 8.—Young bitch. Poorly nourished. Weight about 4 kilos. Mucous membranes pale.

February 25. Median incision 6.5 cm. long. Uterus very small, the oviducts slender, cord-like structures. Evisceration of both ovaries, the uterus and oviducts *in toto*. There was very free bleeding from all the vessels. Immediate closure in layers. But slight change in pulse during operation. Fifteen minutes later dog appeared to be having a hard, shaking chill. Was conscious, but not able to hold up her head.

February 26. Dog is bright, but moves about very little.

March 1. Dog appears to be gaining rapidly. Is now walking about her cage. Very anemic. Ether anesthesia. Abdomen reopened through previous incision. No free blood in peritoneal cavity. Omentum and intestines adherent in places to bladder, pelvic wall and rectum; all easily separated. Around the stump of the uterus a small blood-clot was adherent. No other clots present. Forcible manipulations of the stumps of the uterine vessels produced no active bleeding, only an oozing. Dog went into sudden collapse. Revived by artificial respiration.

Dog No. 9.—In good condition. Weight about 4.5 kilos.

February 26. Ether anesthesia. Median incision 6.5 cm long. Total evisceration of intra-abdominal genitalia as in previous animal. Profuse hemorrhage. Immediate closure in layers. Mucous membranes became greatly blanched. At close of operation pulse-rate was 180, shortly afterward becoming almost imperceptible. Soon after reaching bed dog was conscious, but made no attempt to move.

March 2, Dog is bright and fairly active. Mucous membranes quite pale. Ether anesthesia. Abdomen reopened through previous incision. No fluid or clotted blood present in peritoneal cavity. Stump of corpus uteri brought up and found surrounded by a small clot. No distinct pulsation to be made out in uterine vessels. Well-marked oozing caused by active manipulations of pelvic structures, increased by freshening cut surfaces of previous operation. Closure in layers. Pulse rapid, but of good volume at end.

Dog. No. 10.—In excellent condition. Weight 17.5 kilos.

March 15. Ether. Median incision. Uterus very small for so large an animal (has never been pregnant). Uterine vessels cut on both sides. Bleeding by no means so free as in previous cases. Closure in layers. Pulse good at close.

March 18. Dog appears as well as before operation.

Dog No. 11.—In fairly good condition. Weight about 6 kilos. Considerable enlargement of both thyroids.

March 18. Ether. Median incision. Pelvic organs normal. Uterine vessels of average size. Cut on both sides. Bleeding very free. Immediate closure. Pulse rapid, but of pretty good volume.

March 19. Dog to-day is bright and playful. Abdomen reopened under ether; one to three drams of bloody fluid present, and a small blood-clot on each broad ligament at site of cut ends of uterine vessel. Removal of clot on right side brought on active arterial hemorrhage. Genital organs now excised *in toto*, the corpus uteri being cut across below level of previous division of uterine vessels. There was profuse bleeding, probably two ounces escaping from abdominal cavity before closure was made. At the end of operation pulse was rapid and of small size. Mucous membranes greatly blanched. Dog able to hold up her head on reaching cage, but making no attempt to rise.

March 20. This morning dog appears to have recovered well from yesterday's operation. Gets around well. While ether was being administered again dog ceased breathing, and all measures for resuscitation failed. About 6 c.c. of fluid and clotted blood found between bladder and intestines. Intestinal serosa pale.

Dog No. 12.—Young bitch in fairly good condition. Weight 5 kilos.

March 21. Ether. Median incision. Uterus quite small, but vessels of good size for age of dog. Right uterine vessels cut. Free arterial hemorrhage. Immediate closure. Pulse of good volume, not very rapid.

March 22. Dog all right to-day. Ether. Abdomen reopened; 8–10 c.c. of bloody fluid and blood-clots present. Left uterine vessels were cut and bled freely.

March 23. Dog seems rather weak to-day, but is able to get around well. Abdomen reopened. About the same amount of blood present as found yesterday. Manipulation of uterus and broad ligaments caused fresh bleeding from uterine vessels. Dog conscious at close.

March 26. Dog somewhat dull to-day. Incision infected and gaping. Killed by forced anesthesia. Several cubic centimeters of purulent fluid found in pelvis. (Portion of femoral vein removed for study.)

Dog No. 13.—In good condition. Weight about 9 kilos.

March 25. The abdomen was opened in the median line. Each oviduct was occupied by four fetal sacs. It was estimated that the dog was about one-third along with her pregnancy, the period corresponding to the third month of gestation in the human being. The blood-vessels in the broad ligament were dilated, the uterine artery measuring 2 mm. in diameter at the junction of the oviduct and the body of the uterus. The right uterine vessels were incised at this point, the bleeding was profuse, and the abdomen was closed while the bleeding was going on. After the closure of the abdominal incision the femoral pulse could just be made out. The mucous membranes were very pale. Fifteen minutes later the dog lay stretched out with her eyes open and breathing quietly, but the femoral pulse could not be made out.

March 26. The dog appears dull, but walks around without any difficulty. Pulse small, 140 to the minute. She was given a subcutaneous infusion of 200 c.c. of normal saline solution.

March 27. Condition of dog good. Pulse 104, regular and of fairly good size. Abdomen was reopened and several cubic centimeters of bloody fluid and clots were found. The proximal ends of the cut uterine vessels were closed, but good pulsation was present in the artery. The fetal sacs of the left side were brought out and opened with longitudinal incisions, which were further torn apart with forceps. These tears were made from the dorsal sac inward on the inferior, the superior, the anterior, and the posterior surfaces of the oviduct respectively. This procedure was followed by rather free bleeding from one torn sac. The abdomen was closed. One hour following the operation the dog was still prostrated—with a pulse 120, but of fairly good volume.

March 28. Dog in excellent spirits, quite active. Abdomen reopened under ether narcosis. A small quantity of fluid and clotted blood present. Good pulsation present in proximal stump of right uterine artery. Distal portions of the right vessels severed again and the fetal sac adjacent to the body of the uterus on this side torn apart. All the left sacs were again cut open in different places, and the left uterine vessels were severed. There was the usual free hemorrhage. Dog conscious on reaching bed, pulse very rapid and small.

April 2. Dog rather dull yesterday and to-day, but gets around well. Has shown no symptoms of pain. This morning the abdomen was reopened for the fourth time within a period of nine days. Several cubic centimeters of dark bloody fluid were present. Bladder much distended. Omentum adherent to fetal sacs. The left uterine vessels were thrombosed in their severed ends. Definite pulsation in the artery could not be made out on either side. The uterus, together with the fetal sacs, was now removed. The bleeding from the freshly cut uterine and ovarian vessels was very free. Abdomen closed. At the end of the operation the femoral pulse was 140 to 150, irregular and small. Mucous membranes much blanched. A tight binder was placed around the abdomen and the dog left in the Trendelenburg position. Three hours later the condition was about the same. Three hundred and twenty-five cubic centimeters of a saline solution given subcutaneously, with slight improvement of the pulse.

April 3. Twenty-four hours after the last operation the dog was found in much better condition, able to be on her feet and taking nourishment readily. Pulse 120, regular and of fairly good volume.

Dog No. 14.—Small fox-terrier bitch, pup, black and white, with yellow face. Weight 10 pounds.

February 10, 1908. 12.00, anesthetic started. Pulse 160. Two inch median incision made. Right ovary, uterus and oviducts excised. No ligatures placed. Wall incision closed in layers. Pulse at end of operation 140. Dog placed in pen.

5.00, Pulse 160. Dog drinking water this afternoon, and when taken out of pen walks back.

February 11. Dog eating and apparently in good condition, but remains rather quiet.

February 13. Dog sluggish, eats a little, drinks water, walks about a little, but seems to want to be quiet.

February 15. Dog ate last night apparently as usual. Found dead this morning.

Autopsy. Wound looks clean but has not united firmly. Under the incision there is a mass of clotted bloody fluid matting the bowels together, and uniting them to abdominal wall. No firm adhesions found here. There is some free dark bloody fluid in abdomen. (Smears taken later from this and stained, showed long coarse square-ended bacilli. Cultures on agar showed no growth.) The intestines are matted together in semi-solid blood-clots. The omentum is matted into a mass on the left side. Intestines clear. Liver, spleen and pancreas appear normal. Heart and lungs normal. The uterine stump is covered with a firm blood-clot and a few fine adhesions.

We have recently carried out two experiments to determine what effect would be produced by cutting the uterine veins alone. It has been said that the bleeding from a ruptured ectopic is for the most part venous in character, and will keep up indefinitely if the vein alone is injured. In neither of our experiments were we able to prove that such is the case, as in each instance as will be seen by consulting the details of the experiments, the dogs recovered.

The two dogs experimented upon are numbered 30 and 31 respectively, as the experiments were carried out recently, but they can best be introduced in this series of experiments.

Dog. No. 30.—June 6, 1908. Brindle bull bitch. Weight 17 pounds.

11.15. Pulse 128.

12.00. Anesthetic started.

12.15. Pulse 180. Resp. 80. Hemoglobin 88.

12.17. Abdominal incision made.

12.20. Pulse 160. Resp. 96. Hemoglobin 88.

12.21. Left uterine artery cut and tied. Right uterine veins cut—the artery being left intact.

12.25. Pulse 168. Resp. 84.

12.30. Pulse 160. Resp. 92.

12.38. Pulse 180. Resp. 90. Hemoglobin 84.
12.45. Abdomen closed. Morph. sulph. gr. ½ given hypo.
12.55. Hemoglobin 80.
1.00. Pulse 108. Resp. 88.
1.45. Pulse 104. Resp. 44. Hemoglobin 82.

June 7. 2 P. M. Dog active, running about so that bandages are completely off. Wound left unprotected. Hemoglobin 82.

June 12. Uneventful recovery.
June 23. Perfectly recovered.

Dog. No. 31.—June 16, 1908. Long black-haired bitch. Weight 16 pounds.

11.15. Anesthetic started.
11.30. Pulse 180. Resp. 40. Hemoglobin 100.
11.35. Hemoglobin 102.
11.37. Incision made.
11.40. Pulse 132. Resp. 32.
11.46. Right uterine vein cut.
11.50. Pulse 136. Resp. 28.
11.52. Left uterine vein cut. Both arteries left intact and pulsating.
11.55. Pulse 102. Resp. 20. Hemoglobin 95.
12.03. Abdomen closed.
12.10. Morph. sulph. gr. 1 hypo.
12.25. Hemoglobin 94.
1.35. Pulse 160. Resp. 20. Hemoglobin 94.
June 17. Dog active—eating.
June 23. Uninterrupted recovery.

Résumé.—In this series we have sixteen observations.

I would like to call attention to the experiments carried out in Dogs No. 7 and 13 as they are of rather unusual interest.

In Dog No. 7 after cessation of the bleeding we injected subcutaneously 400 c.c. of normal salt solution. This procedure seemed to exercise a general beneficial result but brought about no recurrence of the hemorrhage. This observation would go toward refuting the view of Fritsch, who says "To give subcutaneous saline infusions before the operation is wrong. I advise them directly after the operation."

Dog No. 13, who was about one-third along with her pregnancy, was operated upon four times within a period of nine days. At the first operation the right uterine vessels were incised. At the second operation (two days after the first) the fetal sacs on the left side were opened by longitudinal incisions. At the third operation (day after second operation) the distal portions of the right uterine vessels were severed again, and the fetal sacs on the right side were torn open, the left sacs were again cut open in different places and the left uterine vessels were severed. At the fourth operation (five days after the third operation) the uterus together with the fetal sacs were removed. (No vessels were tied or clamped at any of the operations). Twenty-four hours after the last operation the dog was able to be on her feet and took nourishment readily.

Series No. 2. Division of the Uterine Vessels Producing Shock. Secondary Operation on Dog while in a Condition of Shock.

Dog No. 14.—February 7. Black and white short-haired bitch, spotted black and white face. Weight 26 pounds.

9.55. Anesthetic started.

10.25. Operation started. Pulse 200. Resp. 88. Three-inch median incision. Oviducts and uterus very vascular, bladder distended.

10.45. Right uterine vessels cut. Pulse 204.

10.50. Apex beat of heart cannot be felt.

10.55. Apex beat of heart cannot be felt. Mucous membranes paling. Resp. 140. Anesthetic stopped.

10.56. Resp. 72; Cheyne-Stokes type.

11.00. Apex beat not palpable. Tongue and mucous membranes gray.

11.05. Apex beat not palpable. Tongue and mucous membranes gray. Dog seems to be coming out from anesthetic.

11.10. Dog well out from under anesthetic. Tongue blanched. Pulse not perceptible.

11.15. Apex beat feeble. Pulse about 140. Color of mucous membranes better.

11.20. Abdomen opened again. Three ounces of bloody fluid sponged out. Bladder tapped, emptied and dropped back into cavity. The oviducts and incised vessel manipulated. The cut vessels were found oozing, but not markedly.

11.23. Apex beat feeble. Resp. 64; good.

11.24. Apex beat feeble. Resp. 100.

11.25. Pulse taken at left uterine artery, 200 per minute.

11.30. Apex beat feeble. Resp. good. Mucous membranes improving in color.

11.40. Apex beat palpable, but rate cannot be counted. Resp. 32. Apparently failing. Artificial respirations begun and continued until 11.55.

11.55. Dead. A fairly good-sized clot was found at point at which right uterine vessels had been severed.

Résumé. In this dog the right uterine vessels were severed and the abdomen was closed while the vessels were bleeding. After an interval of 35 minutes the dog's pulse was 204, and it fell to 140 before the abdomen was opened again. On opening the abdomen the second time we manipulated the abdominal contents in very much the same manner as would be carried not in doing an operation for a ruptured ectopic pregnancy.

The abdomen was then closed. In thirty-five minutes after this the dog expired, either from the effects of the operation, or of the anesthetic, or from a combination of these factors. This experiment, while only a single observation, is at least suggestive that the addition of shock to shock—which is precisely what we bring about when we submit a woman to an immediate operation for ruptured tubal pregnancy—is very likely to prove fatal.

Series No. 3. Division of the Uterine Vessels and Observations upon the Pulse, Respirations, Blood-pressure and Hemoglobin.

Dog No. 18.—February 28. Brown long-haired bitch pup. Weight 12 pounds. Before starting anesthetic pulse 132.

11.20. Anesthetic started.
11.40. Pulse 162. Resp. 46
12.00. Pulse 180. Resp. 52. Hemoglobin 120.

Mercury manometer connected with femoral artery. Blood-pressure 130 mm. of mercury.

12.05. Pulse 182. Resp. 80.
12.06. Abdominal incision made.
12.10. Morph. sulph. gr. ½ hypo. Uterine vessels on one side were cut.
12.15. Blood pressure 100 mm. of Hg.
12.20. Pulse 108. Resp. 60. Hemoglobin 98.
12.25. Pulse 124. Resp. 66.
12.30. Pulse 104. Resp. 120.
12.35. Pulse 132. Resp. 180. Hemoglobin 110.
12.40. Pulse Resp. 108.
12.45. Pulse 134. Resp. 162. Blood-pressure 90 mm. of Hg.
12.50. Pulse 120. Resp. 168. Hemoglobin 98
12.52. Abdomen reopened and clot removed from cut end of vessels.
1.15. Pulse 128. Resp. 168.
1.30. Morph. sulph. gr. ½ hypo.
1.40. Abdominal wall closed.
3.00. Dog walking around.

February 29. Dog appears to be feeling fairly well to-day.

March 3. Dog no very active. Acts as if she were toxic.

March 4. Died to-day. Abdominal wound gangrenous, having completely broken down. No free fluid nor blood in abdominal cavity. Over the cut end of vessels there is a well-formed clot. Between the uterus and bladder there are a few fine adhesions. Liver and spleen enlarged and soft. Other organs apparently normal.

Dog. No. 15. February 12. White bull bitch. Weight 34 pounds. Before operation pulse 180–200. Hemoglobin 127.

11.32. Both uterine and ovarian vessels cut.
11.35. Morph, sulph. gr. 1 hypo.
11.48. Pulse 180. Resp. 60.
11.55. Pulse 152. Resp. 90 (shallow).
12.00. Hemoglobin 115.

12.10. Pulse 140. Resp. 72.

12.15. Pulse 132. Resp. 60. Hemoglobin 115.

12.25. Morph. sulph. ½ gr. hypo. Pulse 132. Resp. 50.

12.30. Abdomen reopened and six ounces of bloody fluid sponged out.

12.35. Pulse 140.

12.45. Pulse 136. Resp. 30.

1.00. Pulse 120. Resp. 30.

Dog remained dazed and sleepy all afternoon.

February 13. Dog lively. Seems to be feeling well.

February 17. Dressings removed. Incision broken down. Edges edematous and a bloody serous fluid discharging from wound. Rbc. 6,956,000. Hemoglobin 110.

February 18. Dog lively, eating, feeling well.

February 20. Wound nearly closed. Dog doing very well.

March 2. Before operation pulse 160.

10.20. Anesthetic started.

10.35. Pulse 186. Resp. 28.

10.45. Morph. sulph. gr. ½ hypo.

10.50. Ether discontinued.

11.00. Began opening neck to insert cannula in left carotid artery. Pulse 198. Resp. 42. Hemoglobin 130.

11.10. Morph. sulph. gr. ½ hypo. Resp. 28.

11.20. Mercury manometer connected with left carotid artery. Blood pressure 120 mm. of mercury.

11.25. Abdominal incision made.

11.30. Morph. sulph. gr. ½ by hypo.

11.32. Right uterine vessels cut on uterine stump.

11.34. Abdominal wall closed with hemostatic forceps.

11.37. Pulse 180. Resp. 42. Blood-pressure 120 mm. of Hg. Hemoglobin 120.

11.45. Pulse 172. Resp. 48.

11.50. Blood-pressure 110. Hemoglobin 115.

12.15. Abdomen opened. Pretty well filled with bloody fluid. A fairly well organized clot found over the cut end of right uterine vessels. There was no active bleeding until after pelvic contents had been manipulated, then the blood welled up out of abdominal incision.

12.25. Closure of abdominal wound begun.

12.30. Morph. sulph. gr. ½ hypo. Pulse 168. Resp. 32. Blood-pressure 110. Hemoglobin 115. Dog remained sleeping remainder of afternoon.

March 3. Dog lies quietly this morning.

March 5. Dog feeling well, walking around.

March 15. Dog perfectly recovered.

April 23. Hemoglobin 105 per cent.

Résumé. In Dog No. 1 of this series the blood-pressure had dropped from 130 mm. of mercury to 100 mm. of mercury within five minutes after the uterine vessels had been cut, and in 30 minutes more the blood-pressure was 90 mm. of mercury.

During this period of time the hemoglobin fell in all 22 points (from 120 to 98).

In another experiment (this dog had been operated upon five days previously), both ovarian and uterine vessels having been cut, the hemoglobin fell from 127 to 115 in forty-three minutes. Five days after the operation the hemoglobin was 110. Eleven days afterward a second operation was carried out similar to that upon Dog No. 1 of this series. The blood-pressure which was 120 mm. of mercury, one hour after section of the right uterine vessels, fell to 110. The hemoglobin at the beginnng of the experiment was 130 and fell to 115 an hour after the cutting of the vessel.

As might be supposed the blood-pressure falls slightly and the hemoglobin drops as usual immediately after division of the vessels. As soon, however, as the bleeding ceases the hemoglobin stops going down and remains stationary for a time, and the blood-pressure rises.

Series No. 4. Division of the Vessels and Observations of the Pulse, Respiration and Hemoglobin with Especial Reference to the Time of the Clotting of the Blood.

Dog No. 16.—February 18. Fox-terrier and bull bitch. Weight 16 pounds. Before starting anesthetic pulse 156. Respirations not taken. Hemoglobin 130.

9.55. Anesthetic started.
10.05. Pulse 180. Resp. 60.
10.25. Operation started. Pulse 176. Resp. 68.
10.35. Pulse 160. Resp. 60.
10.37. Left uterine vessels cut. Pulse 176. Resp. 52
10.45. Pulse 200+. Resp. 56.
10.55. Pulse 240?. Resp. 52.
11.00. Morph. sulph. hypo. gr. ½. Hemoglobin 110.
11.05. Pulse 176. Resp. 32.
11.15. Pulse 160. Resp. 28. Hemoglobin 110.
11.30. Pulse 154. Resp. 24. Hemoglobin 110.

Bleeding in pelvis now practically ceased. There are numerous small blood-clots between intestines and bladder and over cut end of left uterine vessels.

11.45. Pulse 140. Resp. 33. Hemoglobin 110.
11.50. Pulse 132. Resp. 32.
11.54. Morph. sulph. gr. ½ by hypo.

11.55. During last fifteen minutes there has been no fresh bleeding. Clots are firmer. Dog is resting quietly. Femoral pulse is regular and of good volume. Pulse and respiration about the same as at 11.50. Four ounces of bloody fluid sponged from abdominal cavity. There is a well-formed clot over the proximal cut end of uterine vessels. Clot removed and active bleeding started again (weight of this clot 1 gram).

12.50. Dog remained sleeping all afternoon.

February 19. Dog takes liquids, but not very active.

February 20. Dog walking around. Has eaten solid food to-day.

Hemoglobin to-day 115.

February 27. Dog's condition has gradually improved, although she is considerably emaciated. Bandages removed to-day leaving open a raw granulating broken down wound.

February 28. Dog was walking around this morning. Found dead this afternoon.

Autopsy. On opening the abdomen three loops of small intestines were found adherent to the abdominal wall immediately under the wound. Abdominal wall incision had completely broken down except the peritoneal layer. Muscle and skin layers widely retracted. No free fluid in abdominal cavity. No blood found. A few fine adhesions behind the bladder. Right uterine vessels seemed normal. Left uterine vessels thrombosed. Liver somewhat swollen. Other organs appear normal.

Dog No. 17.—February 21. Black and white fox and sky terrier bitch. Weight 21 pounds. Before anesthetic was started pulse 128.

10.30. Anesthetic started (ether).

11.10. Operation started. Hemoglobin 140.

11.15. Anesthetic stopped. Pulse 160. Resp. 56.

11.16. The uterine vessels on both sides cut, the stumps being dropped back into abdominal cavity with catgut guides attached to the broad ligaments.

11.20. Morph. sulph. gr. ½ by hypo. Resp. 48.

11.25. Pulse 196. Resp. 64. Hemoglobin 130.

11.30. Morph. sulph. gr. ½ by hypo.

11.35. Considerable vomiting and straining, then dog became very quiet.

11.35. Pulse 168. Resp. 150. Hemoglobin 125.

11.45. Pulse 200. Resp. 200.

11.50. Pulse 180. Resp. 180. Hemoglobin 125.

12.00. Resp. 150.

12.05. Pulse 156. Resp. 138.

12.10. Pulse 152. Resp. 104.

12.15. Abdomen reopened. Pulse 154. Resp. 66. No bleeding found. There are large clots on the left side. On drawing up the uterus and separating the clot on the left side the bleeding recommences. Same occurs on removing small clot from the right side.

12.30. Pulse 112. Resp. 56.

12.40. Abdominal wall closed.

4.00. Pulse 140. Dog slept all afternoon.

February 22. Dog active and feeling good. Hemoglobin 125. Dog made a very rapid recovery. Skin incision healed perfectly, and this dog was used again April 24 as Dog No. 20.

Résumé. In this series we endeavored to trace some connection between the pulse, respirations and the hemoglobin values and the formation of the blood-clot, or in other words, the cessation of the bleeding.

In the first dog of this series, in eight minutes after the left uterine vessels had been cut the pulse had risen from 200 to 240, and the respirations were 52. In twenty-three minutes after the severance of the vessel the hemoglobin had fallen twenty points, but taken fifteen to thirty minutes later the hemoglobin showed the same reading. After the hemoglobin ceased going down the pulse and respirations began to improve, the pulse going to 154 and the respirations to 24. On reopening the abdomen we found a number of clots lying between the intestines and the bladder and around the cut ends of the vessels. One clot which weighed 1 gram was removed and active bleeding started up again. The abdomen was again closed. On Feb. 28, ten days after the operation; she developed a septic peritonitis from the infected abdominal incision and died.

We have carried out this experiment frequently enough in dogs to make us feel reasonably certain that from the hemoglobin readings alone we can tell the time at which the clot has formed in the vessels. In every instance in which the hemoglobin ceases to go down and the reading remains stationary (and this in our experience always occurs) and the abdomen is reopened a well-formed clot will be found occluding the vessels. I believe that the hemoglobin readings will be found very useful in cases of intra-abdominal hemorrhage from a ruptured ectopic pregnancy, and that when we see that the hemoglobin remains stationary we can feel confident that we are doing the best for the patient in not operating at once.

The experiments in this group of dogs may be divided into three distinct portions: (1) In the first the pulse and respirations become very rapid after the division of the uterine vessels, the pulse becoming in some instances so fast that it is practically impossible to count it. During this time the hemoglobin will fall from 10 to 20 points. This portion of the experiment occupies about 20 minutes. (2) During the next fifteen to twenty minutes the dog looks as if it would die, but the hemoglobin remains practically stationary. If the abdominal cavity is now reopened a well defined blood-clot will be found about the incised vessels and the pedicle, and the bleeding will have ceased. (3) During the third fifteen to twenty minutes the pulse and respiration start to improve again, and the dogs begin to show evidences of reacting. As a rule, from then on the recovery is without incident.

Series No. 5. Division of Vessels, Observations on the Pulse, Respirations and Hemoglobin before and after Bandaging and after Applying Weights to the Lower Abdomen.

Dog. No. 19.—March 13. Small brown short-haired bitch pup. Weight 8 pounds.

10.45. Pulse 190. Resp. 48. Hemoglobin 85–90 per cent.

10.46. Abdominal incision.

10.50. The uterine vessels on both sides cut.

11.00. Abdomen closed (skin clamps used).

11.05. Pulse 200. Resp. 48. Hemoglobin 90. Tight pressure bandages applied.

11.10. Morph. sulph. ½ gr. by hypo. Dog vomited almost immediately.

11.20. Pulse 150. Resp. 20. Hemoglobin 90.

11.35. Pulse 96. Resp. 24.

12.35. Pulse 100. Resp. 12.

3.00. Pulse 108. Resp. 12. Dog drinking water. Pulse very irregular.

March 14. Dog not so quiet. Pulse 160, irregular.

March 15. Dog quiet. Pulse 156, more regular.

March 21. Dog walking around. Wound appears clean. Fresh dressings applied.

March 25. Edges on wound not so clear as on the twenty-first. Fresh dressing.

March 30. Dressing removed. Dog licks wound. Wound looks better.

April 5. Dog emaciated but seems to be doing fairly well.

April 10. Dog emaciated but has considerable abdominal distention.

April 12. Abdomen markedly distended. Skin clamps still in place. Dog not very active. Hemoglobin 90.

Autopsy. Dog killed with ether. Abdominal cavity contains a considerable amount of purulent fluid. Bladder markedly distended. Omentum adherent to abdominal wall along the old incision which had completely healed. Lymphatics of intestines white and stand out distinctly. Liver yellow, fatty, swollen. Spleen soft and swollen. Heart and lungs appear normal. Smears from abdominal fluid show many pus-cells, in some of which a few cocci can be found.

Dog No. 20.—March 13. Brown long-haired bitch pup, white belly. Weight 10 pounds. Pulse before starting anesthetic 168.

11.40. Anesthetic started.

11.42. Pulse 168. Resp. 60.

11.48. Abdominal incision made. Hemoglobin 85.

11.50. Pulse 200. Resp. 92.

11.55. The uterine vessels on both sides cut. Pulse 190. Resp. 80. Hemoglobin 87.

12.00. Morph. sulph. gr. ½ by hypo. Pulse 188. Resp. 68.

12.05. Pulse 144. Resp. 48. Hemoglobin 80.

12.10. Anesthetic stopped and abdomen closed. Pulse 116. Resp. 40.

12.26. (Before pressure bandage was applied.) Pulse 198. Resp. 69.

12.32. (After pressure was applied.) Pulse 220. Resp. 52. Hemoglobin 85.

3.00. Dog drinking water. Pulse 180. Resp. 24.

March 14. 3.00 P. M. Pulse 128, regular. Dog quiet.

March 15. 1 P. M. Pulse 140, regular. Dog quiet.

March 24. Bandage taken off. Wound clean. Dog active and feeling good.

April 12. Dog had been active and doing very well until two days ago when she refused to eat, and on April 11, at 6 P. M. she died.

Autopsy. Incision clean and perfectly united. There are a few adhesions between omentum and abdominal wall along the old wound. No free fluid and no blood in abdominal cavity. Peritoneal surface smooth and apparently clear. Bladder small. Uterine stumps free. No adhesions but tissues about it are somewhat blood-stained. Intestines, spleen, liver, heart, lungs, etc., appear normal.

Dog No. 21.—March 21. Black and tan short-haired bitch, tan muzzle, white throat and four white feet. Weight 16 pounds.

10.30. Anesthetic started. Pulse 88, very irregular.

10.45. Pulse 160. Resp. 32. Hemoglobin 125.

11.20. The uterine vessels on both sides cut.

11.25. Pulse 162. Resp. 56.

11.27. Abdomen closed.

11.30. Light pressure bandage applied. Pulse 132–136. Resp. 48. Hemoglobin 110.

11.50. Pulse 126. Resp. 40.

11.55. Pulse 128. Resp. 30. labored.

12.00. Pulse 144, irregular.

12.05. Pulse 172, regular in force and rhythm. Resp. 20.

12.20. Pulse 136–156. Resp. 14.

12.23. Morph. sulph. gr. ½ by hypo.

12.30. Pulse 148. More regular and better quality. Resp. 12. Hemoglobin 110.

March 22. 5.00 P. M. Dog quiet. Pulse 132.

March 25. Bandage removed. Wound dressed again. Incision looks clean. Doing well. Dog feeling fairly well.

April 25. Dog has made an uninterrupted recovery. Is now well nourished and in very good condition.

Dog No. 22.—March 24. Big long-haired black and white bitch pup. Weight 50 pounds.

10.20. Anesthetic started.

10.30. Pulse 144. Resp. 100.

10.46. Incision made. Hemoglobin 115.

10.50. Hemoglobin 115.

11.06. The uterine vessels on both sides were cut and sutures previously placed for closing abdominal walls were tied as soon as possible; rubber pressure bandage applied.

11.10. Hemoglobin 110.
11.15. Pulse 104. Resp. 32.
11.20. Pulse 200. Resp. 36.
11.27. Pulse 150–152. Resp. 48
11.35. Pulse 128–132. Resp. 24.
11.55. Pulse 132. Resp. 24.
12.05. Dog whining. Hemoglobin 100.
12.15. Pulse 200+. Resp. 20.
12.20. Morph. sulph. gr. 1 by hypo.

March 25. Noon. Pressure bandage removed. Pulse 150 before removing pressure. Pulse 150 after removing pressure. Hemoglobin 100.

March 26. Dog walking around.

March 30. Dog active. Doing very well.

April 15. Dressing removed. Hemoglobin 100.

April 23. Hemoglobin 95.

Dog No. 23.—April 15. Water spaniel bitch. Weight 25 pounds. Before operation pulse 160.

10.25. Incision made. Hemoglobin 108.
10.40. Left uterine vessels cut.
10.45. Pulse 172. Resp. 48.
10.47. Abdomen closed.
10.48. Hemoglobin 95.
10.50. Rubber pressure bandage applied.
10.55. Pulse 156. Resp. 58.
10.56. Hemoglobin 90.
11.15. Pulse 114. Resp. 40. Hemoglobin 85. (?)
11.25. Dog vomiting and whining. Pulse 180. Resp. 28.
11.30. Morph. sulph. ½ gr. hypo. Dog whining.
11.35. Pulse 156. Resp. 28.
11.45. Dog perfectly quiet. Pulse 140. Resp. 28.
12.15. Dog perfectly quiet. Pulse 148. Resp. 20. Hemoglobin 90.
12.30. Dog perfectly quiet. Pulse 154. Resp. 16.
2.10. Pulse 148. Resp. 18.
2.45. Pulse 148. Resp. 24. Hemoglobin 100. (?)
2.55. Dog perfectly quiet.
3.30. Dog perfectly quiet. Hemoglobin 90.
3.40. Dog moving head some. Pulse 140. Resp. 14.
5.00. Dog whining. Pulse 138. Resp. 12. Hemoglobin 90. Legs swollen, edematous, blue and cold.
5.10. Pressure bandage removed.
5.15. Morph. sulph. gr. ½ by hypo.
5.30. Pulse 140. Resp. 20. Hemoglobin 90+. Legs warm, swelling and edema have disappeared. Dog walks, but drags left leg.

April 16. Dog walks about but seems sluggish.

April 17. About the same as yesterday, eating and bowels moving.

April 19. Dog still prefers to be quiet. Bandages removed.

April 25. Dog feeling better.

Dog No. 24.—April 20. Brown short-haired bitch, toes white-tipped. Weight 13 pounds. Pulse before starting anesthetic 164. (Pulse taken through entire experiment, at heart apex with stethoscope.)

10.40. Anesthetic started.

10.52. Incision made.

10.59. The uterine vessels on both sides cut. Pulse 140. Resp. 30. Hemoglobin 125.

11.00. Pulse 154. Resp. 80.

11.01. Closure finished.

11.02. Hemoglobin 125.

11.04. Abdomen compressed with hands, then two-pound weight applied until 11.00.

11.11. Twelve-pound weight applied to abdomen. Pulse 154. Resp. 36.

11.12. Dog vomited. Hemoglobin 115.

11.20. Pulse good volume and quality. Pulse 118. Resp. 24.

11.25. Pulse good volume and quality. Hemoglobin 115.

11.30. Pulse good volume and quality. Pulse 116. Resp. 24.

11.31. Twelve-pound weight removed from abdomen.

11.35. Abdomen reopened. Pedicles drawn up. Clot torn off of cut end of right uterine vessels in drawing up the stump, leaving a pulsating hemorrhage. A firm clot remained over cut end of left uterine vessels. This was removed and the uterus dropped back into abdomen.

11.42. Reclosure of abdomen started. Pulse 116. Resp. 28.

11.47. Pulse 124. Resp. 24.

11.52. Hemoglobin 107.

11.55. Twelve-pound weight again applied to abdomen. Pulse 132. Resp. 16.

11.57. Pulse better volume and quality. Pulse 114. Resp. 16.

12.05. Pulse 128. Resp. 20. Hemoglobin 105.

12.09. Twelve-pound weight removed.

12.10. Pulse 138. Resp. 16.

12.15. Morph. sulph. gr. ½ by hypo.

April 21. Dog walking around.

April 23. Dressings removed.

April 25. Doing very well.

Dog. No. 25.—April 21. Black and white long-haired bitch pup. Weight 12 pounds. (Pulse throughout entire experiment taken at heart apex with stethoscope.)

11.05. Anesthetic started.

11.20. Pulse 200+. Resp. 120. Hemoglobin 98.

11.25. Hemoglobin 98.

11.30. Incision made.

11.33. The uterine vessels on both sides cut.

11.35. Pulse 132. Resp. 96. Hemoglobin 97.

11.36. Abdomen closed and four-pound weight applied.

11.40. Pulse 120. Resp. 62.

11.42. Hemoglobin 88.

11.50. Three and one-half pounds added. Total 7½ pounds. Pulse 120. Resp. 62.

11.55. Pulse 100. Resp. 80. Hemoglobin 88.

12.00. Dog struggling some. Pulse 120. Resp. 80.

12.10. Pulse 120. Resp. 92. Hemoglobin 88.

12.16. Weight removed from abdomen and morph. sulph. gr. ½ given by hypo.

12.20. Pulse 120. Resp. 80.

12.35. Pulse 86. Resp. 140. (?)

2.30. Dog quiet. Pulse 88. Resp. 14.

April 22. Dog walking around.

April 25. Dog doing very well.

Dog No. 26.—April 22. Brown long-haired skye terrier bitch pup. Weight 13½ pounds. Before starting operation pulse 160.

10.20. Anesthetic started. Pulse taken with stethoscope at heart apex.

10.40. Pulse 218. Resp. 80. Hemoglobin 100.

10.50. Pulse 196. Resp. 112.

10.57. Morph. sulph. gr. ¼ hypo.

11.00. Incision made.

11.05. Pulse 160. Resp. 100. Hemoglobin 100.

11.09. Distended bladder tapped.

11.15. The uterine vessels on both sides cut. Pulse 152. Resp. 108.

11.18. Abdomen closed.

11.20. Pulse 140. Resp. 112. Hemoglobin 100.

11.21. Three and three-fourths-pound weight placed on abdomen.

11.22. Resp. 86.

11.27. Hemoglobin 95.

11.30. Pulse 120. Resp. 80, jerky.

11.35. Pulse 120. Resp. 86. Hemoglobin 95.

11.39. Four and three-fourths pounds added (total 8¼ pounds on abdomen).

11.42. Weight on abdomen increased to 10¼ pounds.

11.45. Hemoglobin 95.

11.50. Pulse 100. Resp. 76. Hemoglobin 95.

11.51. All weights removed.

11.56. Pulse 120. Resp. 80. Hemoglobin 95.

12.00. Pulse 120. Good quality. Resp. 68.

12.08. Ten and one-fourth-pound weight again applied to abdomen. Pulse good.

12.16. Pulse 132. Resp. 60.

12.21. Pulse 120. Resp. 44.

12.34. Morph. sulph. gr. ¼ by hypo. Pulse 120. Resp. 44. All weights removed.

April 23. Dog walking around. Condition good.

April 25. Condition good.

Dog No. 27.—April 24. This is the dog used as Dog No. 9. Weight 21 pounds. (Pulse taken with stethoscope at heart apex.)

10.25. Anesthetic started.
10.30. Pulse 140. Resp. 48.
10.40. Hemoglobin 100. (?)
10.45. Abdominal incision.
10.49. Top of uterus and lower portion of both oviducts excised.
10.50. Pulse 132. Resp. 56. Hemoglobin 110.
10.52. Abdominal closure finished and 5 pound weight applied. Pulse 120. Resp. 52.
10.57. Pulse 148. Resp. 44. Hemoglobin 109.
11.03. . Pulse 176. Resp. 50. Hemoglobin 103.
11.10. Pulse 176. Resp. 48. Hemoglobin 103.
11.20. Morph. sulph. gr. ¼ by hypo.
11.25. Four-pound weight added. (total 9 pounds). Pulse 180. Resp. 48.
11.35. Pulse 160. Resp. 36. Hemoglobin 98.
11.40. Pulse 160. Resp. 40. Hemoglobin 103.
11.45. Morph. sulph. gr. ¼ hypo. Pulse 160. Resp. 36.
11.50. Pulse 176. Resp. 32.
12.00. Pulse 192. Resp. 32.
12.10. Pulse 192. Resp. 36.
12.15. All weights removed. Pulse 168. Resp. 36. Pulse irregular.
12.20. Pulse 160. Resp. 36.
12.30. Pulse 156. Resp. 36.
6.00. Dog lies quietly looking around.
April 25. Dog walks around barking.

Résumé.—I wish to call attention to one or two striking experiments in this series.

Dog. No. 19. Weight of dog, 8 pounds. The pulse immediately after both uterine arteries and veins had been cut and before a tight abdominal bandage had been applied, was 200, and the respirations were 48. Forty-five minutes later the pulse was 96 and the respirations were 24. Four hours and ten minutes after the cutting of the uterine vessels, the pulse was 108 and the respirations were 12.

In dog No. 21, the hemoglobin, which before the cutting of the vessels was 125, fell to 110 in 10 minutes. The bandage was then applied to the abdomen and the pulse from 162 and the respirations from 56 came down to 126 and 40 respectively in 20 minutes. Fifty minutes later the pulse varied between 156 and 136, and the respirations between 14 and 20, the hemoglobin still remaining at 110. In two similar experiments a rubber tourniquet was applied after cutting the vessels, and the results were somewhat similar.

In dogs Nos. 17, 18, 20, still more striking results in the pulse, respiration and hemoglobin were obtained by applying weights to the lower abdomen and thus bringing the anterior in more direct apposition with the posterior abdominal wall.

Thus in dog No. 17, which weighed 13 pounds, 12 minutes after cutting the uterine vessels the pulse was 154, the respirations were 36, and the hemoglobin had fallen 10 points. A 12-pound weight was applied to the abdomen and in 8 minutes the pulse had fallen to 118, and the respirations to 24, but the hemoglobin remained stationary. After 10 minutes the pulse was 116 and the respirations were 24. We now opened the abdomen and exposed the vessels; they were surrounded by a firm clot. The clot was removed and the pedicles were dropped back into the abdomen. The pulse and respirations rose again, and the hemoglobin fell to 107–8 points lower than it was before the fresh hemorrhage was started up. The weight was applied again to the abdomen and in 2 minutes the pulse had fallen from 132 to 114. Twelve minutes later the weight was removed again, and immediately the pulse rose to 148.

One other striking experiment in a dog that weighed 12 pounds in this group showed that in 5 minutes after putting a 7½-pound weight on the abdomen, the pulse had fallen from 120 to 100, and the hemoglobin from 98 to 88. This and other experiments with pressure, particularly when it is applied so that the anterior and posterior abdominal walls are brought more closely together, would suggest the application of pressure over the lower abdomen in cases of hemorrhage from a ruptured ectopic pregnancy. This might possibly be carried out by the use of shot or sand bags of known weight, as much weight being employed as the patient could comfortably stand. As our experiments showed, by using the weight in the way just described the results were more striking than when the abdomen was simply bandaged.

Series No. 6.—Division of Uterine Vessels with Dog in the Perpendicular Position; Observations upon Pulse, Respiration and Hemoglobin.

Dog. No. 28.—April 27. Same dog as used April 15 as dog No. 16.

Weight 24½ pounds. Pulse before starting anesthetic 148.
10.20. Anesthetic started.
10.32. Pulse 148. Resp. 68. Hemoglobin 75.
10.35. Hemoglobin 75.

10.38. Incision made. On opening peritoneal cavity no fluid present. A few adhesions between the intestines; posterior portion of the bladder adherent to the uterus. At this point a markedly organized blood-clot. The left uterine vessels thoroughly thrombosed.

10.52. The uterine vessels on both sides cut.

10.54. Ether anesthesia stopped. Morph. sulph. gr. ½ hypo. given and foot of table elevated 2½ feet.

10.56. Foot of table raised to perpendicular position.

11.00. Pulse 200. Resp. 28. Hemoglobin 65.

11.06. Pulse 180. Resp. 28. Hemoglobin 65.

11.12. Hemoglobin 62.

11.16. Pulse 140. Resp. 24. Hemoglobin 61.

11.18. Hemoglobin 61.

11.25. Pulse 160. Resp. 28. Hemoglobin 62.

11.36. Pulse 160. Resp. 28.

11.45. On reopening the peritoneal cavity a well-marked clot seen near bladder and incised uterine vessels. No bleeding at this point. On pulling the tissue and clot forward and separating them the oozing began from the left uterine vessels. The pelvic cavity was free from blood. On making pressure on the upper abdomen bloody fluid came out of incision which had been prolonged up toward head for 2½ to 3 inches. Clot removed from left vessels. Right vessels not disturbed. Three minutes after removing clot from left uterine vessels hemoglobin 55 per cent.

12.30. Table lowered to horizontal position. Pulse 200. Resp. 44.

12.32. Hemoglobin 54.

6.00. P. M. Dog drinking water.

April 28. Dog found dead this morning. On opening the abdomen the intestines are found surrounded by clotted blood. Blood-clots found above and below the liver and throughout the cavity. No new formed adhesions found. Both uterine vessels cut ends covered with blood-clots. Intestines, liver, spleen, heart, lungs, etc., appear normal. Bladder small and walls rather firm.

Dog. No. 29.—April 28. Same dog as that used for No. 13. Weight 23½ pounds. Before starting anesthetic pulse 72.

11.40. Pulse 200. Resp. 44.

11.50. Morph. sulph. gr. ½ by hypo. Ether discontinued.

11.52. Pulse 200+. Resp. 24. Hemoglobin 100.

11.54. Incision made with table in perpendicular position; head down. Bladder found adherent to broad ligament near site of formerly incised vessel. Peritoneum, oviducts and body of uterus pale. Thrombosis in both uterine arteries well organized. Dog whining.

11.58. Both uterine vessels cut. Dog whining less than before vessels were cut.

12.00. Dog vomited. Straining and whining.

12.07. Morph. sulph. gr. ¼ by hypo. Hemoglobin 97.

12.10. Morph. sulph. gr. ¼ by hypo.

12.10. Blood-clot at seat of incision glazed over and vessel pulsates through partially clotted blood. Dog struggling markedly forcing blood and omentum out through the incision.

12.15. Ether given in mask and morph. sulph. gr. ¼ hypo.

12.30. Closure.

12.50. Morph. sulph. gr. ¼ by hypo. Pulse 168. Resp. 20. Hemoglobin 92.

1.30. Pulse irregular, Pulse 132. Resp. 16.

5.00. Dog awake, looking around.

April 29. Dog active.

May 2. Dressing removed. Wound doing well. Dog active and playful.

Résumé.—In the first dog the pulse had fallen from 200 to 180 ten minutes after the dog had been placed in the upright position, but the hemoglobin remained stationary. After twenty minutes the pulse had fallen to 140 and the hemoglobin had also dropped 4 points. In twenty minutes more the pulse had risen to 160, but the hemoglobin remained practically stationary. The abdominal cavity was reopened and a well-defined clot was seen covering the incised tissues; the vessel had ceased to bleed.

In the second dog the vessels were cut with the dog in the perpendicular position, and the bleeding vessel was observed through a strong magnifying glass in order to compare the time of clotting with the hemoglobin readings. The hemoglobin had fallen 3 points seven minutes after incision of the vessels. After 3 minutes more the incised tissues had begun to take on a glazed appearance, and the hemoglobin remained stationary (ten minutes after the uterine vessels had been cut). Three minutes later the dog began to struggle and to force the abdominal contents through the incision, and the hemoglobin taken 40 minutes later showed a fall of 5 points more. One hour and twenty minutes later the pulse was 132, the respirations were 16 (the hemoglobin was not taken). In this experiment we would have to consider the influence that the air would have in helping to cause the clotting of the blood, and as a consequence the slight drop in the hemoglobin index.

CONCLUSIONS.

From these experiments which now number 31 we feel justified more and more in believing that the intra-abdominal hemorrhage, such as is met with in women suffering from collapse after the rupture of an ectopic gestation, is not sufficient in itself to cause a fatal termination in these cases. Death is caused mainly by shock which may be increased by various procedures. The hemorrhage *per se* is rarely, if ever, the sole cause of death.

One experiment goes to show that the superadded shock belonging to immediate operation is likely to be very dangerous.

It will doubtless be maintained by some that our experimental work has shown nothing more than that the dog can withstand a greater loss of blood than a woman—a recognized fact. And yet it seems fair to assume, as will be seen on consulting our protocols, that in many of our experiments, we made the tests sufficiently severe to more than equalize the factor of resistance to the loss of blood in the dog as compared with that of the human being under fairly similar conditions. In other words, taking into consideration this difference in resistance, by cutting both uterine arteries and veins and in some instances both ovarian arteries and veins as well, we subjected our dogs to a risk of bleeding to death as great as or greater than that incurred by the average woman suffering from a ruptured tubal pregnancy.

Our experiments further show that the clotting probably occurs within 15 to 20 minutes after the vessels have been incised, and that the time of clotting can be known by observing the hemoglobin index. The subcutaneous injection of normal salt solution in all probability does not cause a renewal of the hemorrhage. But manipulation of the tissues by disturbing the clot causes the bleeding to start up again, and may thus be mistaken for a continuing hemorrhage.

Our experiments also show that by the use of bandages, but more particularly by the application of more or less weight to the lower abdomen, the pulse is rendered slower and of better quality, and that the hemoglobin is kept up.

It gives me great pleasure to acknowledge the valuable assistance given me in the carrying out of these experiments by my former assistant Dr. M. B. Bonta, and by my present assistants Drs. Frank C. Ainley and Fred W. Hall.

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